PATENT
Customer No. 22,852
Attorney Docket No. 09757.0007-00000

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	
Maria PRAT QUINONES et al.	Group Art Unit: 1625
Application No.: 10/518,496	Examiner: RAHMANI, Niloofar
Filed: September 19, 2005	
For: QUINUCLIDINE DERIVATIVES AND PHARMACEUTICAL COMPOSITIONS CONTAINING THE SAME	Confirmation No. 4930

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

SUBMISSION OF CERTIFIED TRANSLATION OF PRIORITY DOCUMENT

Sir:

Applicants submit herewith a certified translation of Spanish patent application No. P 200201439, filed June 21, 2002. In accordance with 37 C.F.R. § 1.55(a), Applicants hereby perfect claim of priority under 35 U.S.C. § 119 by filing this certified translation.

Please grant any extensions of time required to enter this translation and charge any required fees to our deposit account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: March 7, 2008

By: _____
Carlos M. Téllez
Reg. No. 48,638

IN THE MATTER OF an Application
for a Spanish Patent
in the name of
ALMIRALL PRODESFARMA, S.A.
filed under No. 200201439, and
IN THE MATTER OF an Application
for a European Patent.

RWS Group plc, of Europa House, Marsham Way, Gerrards Cross, Buckinghamshire, England, hereby solemnly and sincerely declares that to the best of its knowledge and belief, the following document, prepared by one of its translators competent in the art and conversant with the English and Spanish languages is a true and correct translation of the Patent Application filed under No. 200201439

by ALMIRALL PRODESFARMA, S.A.

in Spain on 21 June 2002

for "New quinuclidine carbamates and pharmaceutical compositions containing them"

and the Official Certificate attached thereto.

Date: 13 December 2004

E.A. LUCAS
Director
For and on behalf of RWS Group plc

MINISTRY
OF SCIENCE
AND TECHNOLOGY

Spanish Patent and
Trademark Office

OFFICIAL CERTIFICATE

This is to certify that the attached documents are an exact copy of the application for a PATENT of INVENTION number 200201439 submitted to the above Body, dated 21 June 2002.

Madrid, 31 March 2003

[seal]

The Director of the Patents and
Technological Information Department

pp.

[signature]

M. MADRUGA

APPLICATION

[duty stamp and crest]

Spanish Patent and Trademark Office

APPLICATION NUMBER: **P200201439**

(1) FORM:
☒ PATENT OF INVENTION ☐ UTILITY MODEL

DATE AND TIME OF SUBMISSION AT S.P.T.O.: 21 JUN '02 13:41

(2) TYPE OF APPLICATION:
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☐ DIVISIONAL APPLICATION
☐ CHANGE OF FORM
☐ EUROPEAN APPLICATION CONVERSION
☐ PCT: ENTRY INTO THE NATIONAL PHASE

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(5) APPLICANTS: LAST NAMES OR CORPORATE NAME	FORENAME	NATIONALITY	CTY CODE	NID/FIC	NEAC	SMSE
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(8) ☐ THE APPLICANT IS THE INVENTOR
☒ THE APPLICANT IS NOT THE INVENTOR OR SOLE INVENTOR

(9) METHOD OF OBTAINING THE RIGHT:
☒ WORK INVEN. ☐ CONTRACT ☐ SUCCESSION

(10) TITLE OF THE INVENTION:
"NEW QUINUCLIDINE CARBAMATES AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM"

(11) BIOLOGICAL MATERIAL DEPOSITED: ☐ YES ☐ NO

(12) OFFICIAL EXHIBITIONS: PLACE DATE

(13) DECLARATIONS OF PRIORITY: COUNTRY OF ORIGIN	COUNTRY CODE	NUMBER	DATE

(14) THE APPLICANT AVAILS HIMSELF OF DEFERMENT OF PAYMENT OF FEES REFERRED TO IN ART. 162 P.A. 11/86 ☐

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(16) LIST OF ACCOMPANYING DOCUMENTS:
☒ DESCRIPTION, No. OF PAGES: 61
☒ No. OF CLAIMS: 35
☐ DRAWINGS, No. OF PAGES
☐ LIST OF SEQUENCES, No. OF PAGES
☒ ABSTRACT
☐ PRIORITY DOCUMENT
☐ TRANSLATION OF PRIORITY DOCUMENT
☒ REPRESENTATION DOCUMENT
☒ VOUCHER FOR PAYMENT OF APPLICATION FEE
☐ ADDITIONAL INFORMATION SHEET
☐ PROOFS OF DRAWINGS
☐ RESEARCH QUESTIONNAIRE
☐ OTHERS:

SIGNATURE OF APPLICANT OR REPRESENTATIVE
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Antonio Tavira Montes-Jovellar
by my colleague
(SEE ADVICE OVERLEAF)

SIGNATURE OF THE OFFICER
[illegible signature]

NOTIFICATION REGARDING GRANT FEE:
You are advised that this application shall be deemed to have been withdrawn if the grant fee is not paid; you have three months from the publication of the announcement of the grant in the OGIP, plus the ten days stipulated in Art. 81 of R.D. 2245/1986, for payment of the fee.

LEAVE AREAS FRAMED IN RED BLANK

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HIS EXCELLENCY THE DIRECTOR OF THE SPANISH PATENT AND TRADEMARK OFFICE
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Spanish Patent and
Trademark Office

APPLICATION NUMBER
P200201439

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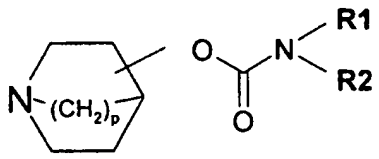
21 June 2002

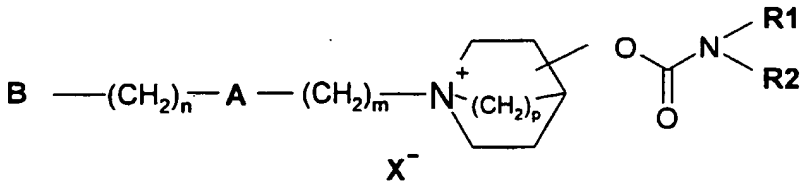
ABSTRACT AND DRAWING

ABSTRACT (Max. 150 words)

New quinuclidine carbamates and pharmaceutical compositions containing them. Carbamates of formula



or pharmaceutically acceptable salts thereof, including quaternary ammonium salts of formula (II)



as well as processes for their preparation, pharmaceutical compositions containing them and their use in therapy as antagonists of M3 muscarinic receptors.

DRAWING

(SEE INFORMATION ON REVERSE)

Mod. 3103

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12

PATENT APPLICATION

21 APPLICATION NUMBER	
P200201439	

PRIORITY DATA			22 DATE OF SUBMISSION
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			62 PATENT FROM WHICH THE PRESENT CASE IS DIVIDED OUT

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51 Int. Cl.

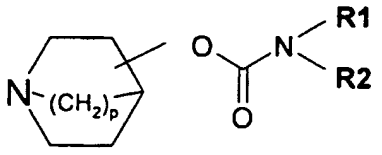
DRAWING (SOLELY FOR THE PURPOSE OF INTERPRETING THE ABSTRACT)

54 TITLE OF THE INVENTION

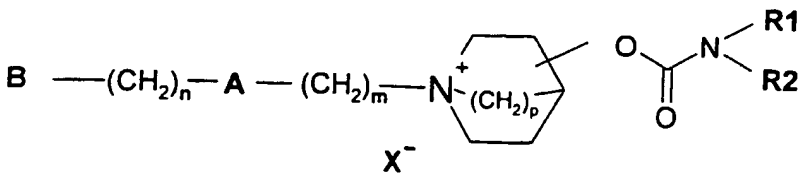
"NEW QUINUCLIDINE CARMAMATES AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM"

57 ABSTRACT

New quinuclidine carbamates and pharmaceutical compositions containing them. Carbamates of formula



or pharmaceutically acceptable salts thereof, including quaternary ammonium salts of formula (II)



as well as processes for their preparation, pharmaceutical compositions containing them and their use in therapy as antagonists of M3 muscarinic receptors.

Mod 3106i

FIRST PAGE OF THE SPECIFICATION

NEW QUINUCLIDINE CARBAMATES AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

This invention relates to new therapeutically useful quinuclidine carbamate derivatives, to processes for their preparation and to pharmaceutical compositions containing them.

The new structures according to the invention are antimuscarinic agents with a potent and long lasting effect. In particular, these compounds show high affinity and selectivity for muscarinic M3 receptors over M2 receptors. The M3 subtype of muscarinic receptor is present in glands and smooth muscle and mediates the excitatory effects of the parasympathetic system on glandular secretion and on the contraction of visceral smooth muscle (Chapter 6, *Cholinergic Transmission*, in H.P. Rang et al., *Pharmacology*, Churchill Livingstone, New York, 1995).

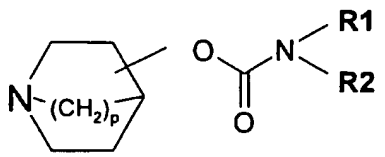
M3 antagonists are known to be useful for treating diseases characterized by an increased parasympathetic tone, by excessive glandular secretion or by smooth muscle contraction (R.M. Eglen and S.S. Hegde, (1997), Drug News Perspect., 10(8):462-469).

Examples of this kind of diseases are respiratory disorders such as chronic obstructive pulmonary disease (COPD), bronchitis, bronchial hyperreactivity, asthma, cough and rhinitis; urological disorders such as urinary incontinence, pollakiuria, neurogenic or unstable bladder, cystospasm and chronic cystitis; gastrointestinal disorders such as irritable bowel syndrome, spastic colitis, diverticulitis and peptic ulceration; and cardiovascular disorders such as vagally induced sinus bradycardia (Chapter 7, *Muscarinic Receptor Agonists and Antagonists*, in *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 10th edition, McGraw Hill, New York, 2001).

The compounds of the invention can be used alone or in association with other drugs effective in the treatment of these diseases. For example, they can be administered in combination with β_2-agonists, steroids, antiallergic drugs, phosphodiesterase IV inhibitors and/or leukotriene D4 (LTD4) antagonists for simultaneous, separate or sequential use in the treatment of a respiratory disease.

The present invention provides new quinuclidine carbamate derivatives with potent antagonist activity for muscarinic M3 receptors, which fall under the general structure described in formula (I) or are pharmaceutically acceptable salts thereof, including quaternary salts of formula (II).

Formula (I) represents a carbamate of the following general structure:



(I)

wherein

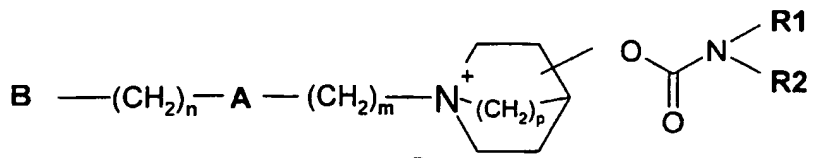
R1 represents a group selected from phenyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, benzyl, furan-2-ylmethyl, furan-3-ylmethyl, thiophen-2-ylmethyl, and thiophen-3-ylmethyl;

R2 represents a group selected from optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkynyl, saturated or unsaturated cycloalkyl, saturated or unsaturated cycloalkylmethyl, phenyl, benzyl, phenethyl, furan-2-ylmethyl, furan-3-ylmethyl, thiophen-2-ylmethyl, thiophen-3-ylmethyl, pyridyl, and pyridylmethyl; wherein the carbocyclic moieties in the cycloalkyl, cycloalkylmethyl, phenyl, benzyl or phenethyl groups can be optionally bridged or fused to another saturated or unsaturated aromatic carbocyclic moiety or to a cyclic moiety comprising carbon atoms and 1 or 2 oxygen atoms;

the cyclic groups present in R_3 and R_4 being optionally substituted by one, two or three substituents selected from halogen, straight or branched, optionally substituted lower alkyl, hydroxy, straight or branched, optionally substituted lower alkoxy, -SH, straight or branched, optionally substituted alkylthio, nitro, -NR'R", $-CO_2R'$, -C(O)-NR'R", -N(R'")C(O)-R', -N(R'")-C(O)NR'R" or wherein R', R" and R'" each independently represents a hydrogen atom or a straight or branched, optionally substituted lower alkyl group or R' and R" together with the atom to which they are attached form a cyclic group;

p is 1 or 2 and the carbamate group is at positions 2, 3 or 4 of the azabicyclic ring,

and pharmaceutically acceptable salts thereof, including quaternary ammonium salts of formula (II)



(II)

wherein R1, R2 and p are as defined above;

m is an integer from 0 to 8;

n is an integer from 0 to 4;

A represents a group selected from $-CH_2-$, -CH=CR'-, -CR'=CH-, -CR'R''-, -C(O)-, -O-, -S-, -S(O)-, $-S(O)_2-$ and –NR'-, wherein R' and R'' are as defined above;

B represents a hydrogen atom, or a group selected from straight or branched, optionally substituted lower alkyl, hydroxy, straight or branched, optionally substituted lower alkoxy, cyano, nitro, -CH=CR'R'', -C(O)OR', -OC(O)R', -SC(O)R', -C(O)NR'R'', -NR'C(O)OR'', -NR'C(O)NR'', cycloalkyl, phenyl, naphthalenyl, 5,6,7,8-tetrahydronaphthalenyl, benzo[1,3]dioxolyl, heteroaryl or heterocyclyl; R' and R'' being as defined above; and wherein the cyclic groups represented by B are optionally substituted by one, two or three substituents selected from halogen, hydroxy, straight or branched, optionally substituted lower alkyl, phenyl, -OR', -SR', -NR'R'', -NHCOR', -CONR'R'', -CN, $-NO_2$ and -COOR'; R' and R'' being as defined above;

X^- represents a pharmaceutically acceptable anion of a mono or polyvalent acid;

including all stereoisomers of formulae (I) or (II) and mixtures thereof;

with the proviso that the compound of formula (I) is not one of

Diphenylcarbamic acid 1-azabicyclo[2.2.2]oct-3-yl ester
Ethylphenylcarbamic acid 1-azabicyclo[2.2.2]oct-3-yl ester.

Further objectives of the present invention are to provide processes for preparing said compounds; pharmaceutical compositions comprising an effective amount of said compounds; the use of the compounds in the manufacture of a medicament for the treatment of diseases susceptible of being improved by antagonism of M3 muscarinic receptors; and methods of treatment of diseases susceptible to amelioration by antagonism of M3 muscarinic receptors, which methods comprise the administration of the compounds of the invention to a subject in need of said treatment.

In the compounds of the invention it is preferred that at least one of R1 or R2 be substituted. Particularly preferred compounds of formula (I) or (II) are those wherein when the cyclic group present in R1 is unsubstituted or has only one substitutentsubstituent, R2 has at least one substituent. Also preferred are compounds wherein when R2 is not substituted the cyclic group present in R1 has at least two substituents.

J. L. G. Nilsson et al. describe in Acta Pharm. Suecica, 5:71-76 (1968) a group of quinuclidine carbamate derivatives having antimalarial activity, among which diphenylcarbamic acid 1-azabicyclo[2.2.2]oct-3-yl ester and ethylphenylcarbamic acid 1-azabicyclo[2.2.2]oct-3-yl ester are mentioned.

WO 02/00652 discloses a group of compounds which fall under the general structure of formula (I) or (II). The specific compounds disclosed in that application are excluded from the present invention.

Thus, in those compounds of formula (I) as described above, wherein

p is 2;

the carbamate group is attached at position 3 of the azabicyclic ring;

and R1 is an unsubstituted indanyl group or a phenyl group, which is optionally substituted with one or two substitutentsubstituents selected from chlorine, fluorine, bromine, methyl, hydroxy and cyano;

then R2 cannot be one of: unsubstituted cyclopropylmethyl; unsubstituted cyclobutylmethyl; unsubstituted cyclopentylmethyl; cyclohexylmethyl optionally

substituted with a methyl or an isopropenyl group; unsubstituted cyclohexenyl; unsubstituted norbornenyl; unsubstituted bicyclo[2.2.1]heptanyl; unsubstituted benzo[1.3]dioxolyl; unsubstituted 2,3-dihydrobenzo[1.4]dioxinyl; unsubstituted benzyl; a benzyl group which is substituted with one or two substituents selected from fluorine, chlorine, bromine, methoxy, methyl, trifluoromethyl, ethyl, tertbutyl, hydroxy, hydroxymethyl, cyano, aminocarbonyl, trifluoromethoxy, benzyloxy, isopropyloxy; and a benzyl group which is substituted with three fluorine atoms.

Further, in those compounds of formula (II) as described above wherein

p is 2;

the carbamate group is attached at position 3 of the azoniabicyclic ring having (3R)-configuration;

R1 is a phenyl group which is optionally substituted with a fluorine atom or a methyl group;

R2 is an unsubstituted cyclohexylmethyl group or a benzyl group which is optionally substituted with one or three fluorine atoms;

and X^- is iodine;

then, the sequence $B\text{-}(CH_2)_n\text{-}A\text{-}(CH_2)_m$- cannot be a methyl group.

More specifically, the following compounds are explicitly excluded from the scope of the invention:

(3R)-3-(Benzylphenylcarbamoyloxy)-1-methyl-1-azoniabicyclo[2.2.2]octane iodide
(3R)-3-[(4-Fluorobenzyl)phenylcarbamoyloxy]-1-methyl-1-azoniabicyclo[2.2.2]octane iodide
(3R)-3-(Benzyl-o-tolylcarbamoyloxy)-1-methyl-1-azoniabicyclo[2.2.2]octane iodide
(3R)-1-Methyl-3-[o-tolyl-(2,4,5-trifluorobenzyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane iodide
(3R)-3-[(4-Fluorobenzyl)-m-tolylcarbamoyloxy]-1-methyl-1-azoniabicyclo[2.2.2]octane iodide

(3R)-3-[Benzyl-(2-fluorophenyl)carbamoyloxy]-1-methyl-1-azoniabicyclo[2.2.2]octane iodide

(3R)-3-[Cyclohexylmethyl-(2-fluorophenyl)carbamoyloxy]-1-methyl-1-azoniabicyclo[2.2.2]octane iodide.

As used herein, an alkyl, alkenyl or alkynyl group or moiety can be straight or branched, and is typically a lower alkyl, alkenyl or alkynyl group. A lower alkyl group contains 1 to 8, preferably 1 to 6, carbon atoms. Examples include methyl, ethyl, propyl, including i-propyl, butyl, including n-butyl, sec-butyl and tert-butyl, 1-methylbutyl, 1-ethylpropyl, 1,2-dimethylpropyl, n-hexyl or 1-ethylbutyl groups. More preferably a lower alkyl group contains from 1 to 4 carbon atoms. A lower alkenyl or alkynyl group contains 2 to 8, preferably 2 to 6, carbon atoms. Examples include vinyl, allyl, 1-propenyl, 4-pentenyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl or 3-butynyl groups. More preferably, a lower alkenyl or alkynyl group contains 2 to 4 carbon atoms.

Optionally substituted lower alkyl, alkenyl or alkynyl groups mentioned herein include straight or branched lower alkyl, alkenyl or alkynyl groups as defined above, which may be unsubstituted or substituted in any position by one or more substituents, for example by 1, 2 or 3 substituents. When two or more substituents are present, each substituent may be the same or different. The substituent(s) are typically halogen atoms, preferably fluorine atoms, and hydroxy or alkoxy groups.

Alkoxy and alkylthio groups mentioned herein are typically lower alkoxy and alkylthio groups, that is groups containing from 1 to 8, preferably 1 to 6 and more preferably 1 to 4 carbon atoms, the hydrocarbon chain being branched or straight and optionally substituted in any position by one or more substituents, for example by 1, 2 or 3 substituents. When two or more substituents are present, each substituent may be the same or different. The substituent(s) are typically halogen atoms, most preferably fluorine atoms, and hydroxy groups. Preferred optionally substituted alkoxy groups include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, sec-butoxy, t-butoxy, trifluoromethoxy, difluoromethoxy, hydroxymethoxy, 2-hydroxyethoxy or 2-hydroxypropoxy. Preferred optionally substituted alkylthio groups include methylthio, ethylthio, n-propylthio, i-propylthio, n-butylthio, sec-butylthio, t-butylthio, trifluoromethylthio, difluoromethylthio, hydroxymethylthio, 2-hydroxyethylthio or 2-hydroxypropylthio.

Cyclic groups mentioned herein include, unless otherwise specified, carbocyclic and heterocyclic groups. The cyclic groups can contain one or more rings. Carbocyclic groups may be aromatic or alicyclic, for example cycloalkyl groups. Heterocyclic groups also include heteroaryl groups.

Cycloalkyl groups and alicyclic groups mentioned herein, unless otherwise specified, typically contain from 3 to 7 carbon atoms. Cycloalkyl groups and alicyclic rings of 3 to 7 carbon atoms include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

As used herein an aromatic group typically contains from 5 to 14, preferably 5 to 10 carbon atoms. Examples of aromatic groups include phenyl and naphthalenyl.

A heterocyclic or heteroaromatic group mentioned herein is typically a 5 to 10 membered group, such as a 5, 6 or 7 membered group, containing one or more heteroatoms selected from N, S and O. Typically, 1, 2, 3 or 4 heteroatoms are present, preferably 1 or 2 heteroatoms. A heterocyclic or heteroaromatic group may be a single ring or two or more fused rings wherein at least one ring contains a heteroatom. Examples of heterocyclic groups include piperidyl, pyrrolidyl, piperazinyl, morpholinyl, thiomorpholinyl, pyrrolyl, imidazolyl, imidazolidinyl, pyrazolinyl, indolinyl, isoindolinyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolizinyl, isoindolyl, indolyl, indazolyl, purinyl, quinolizinyl, isoquinolyl, quinolyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, quinuclidinyl, triazolyl, pyrazolyl, tetrazolyl and thienyl. Examples of heteroaromatic groups include pyridyl, thienyl, furyl, pyrrolyl, imidazolyl, benzothiazolyl, pyridinyl, pyrazolyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolyl, indazolyl, purinyl, quinolyl, isoquinolyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, triazolyl and pyrazolyl.

As used herein a halogen atom includes a fluorine, chlorine, bromine or iodine atom, typically a fluorine, chlorine or bromine atom.

In the quaternary ammonium compounds of the present invention, including those represented by formula (II), an equivalent of an anion (X^-) is associated with the positive charge of the N atom. X^- may be an anion of various mineral acids such as, for example, chloride, bromide, iodide, sulphate, nitrate, phosphate, or an anion of an organic acid such as, for example, acetate, trifluoroacetate, maleate, fumarate, citrate, oxalate, succinate, tartrate, malate, mandelate, methanesulphonate and

p-toluenesulphonate. X^- is preferably an anion selected from chloride, bromide, iodide, sulphate, nitrate, acetate, trifluoroacetate, methanesulphonate, maleate, oxalate or succinate. More preferably X^- is chloride, bromide, trifluoroacetate or methanesulphonate.

Preferred compounds of formula (I) according to the invention as defined above are those wherein R1 represents a group selected from 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, benzyl, furan-2-ylmethyl, furan-3-ylmethyl, thiophen-2-ylmethyl, thiophen-3-ylmethyl; the cyclic groups present in R1 being optionally substituted by one, two or three substituents selected from halogen, straight or branched, optionally substituted lower alkyl, hydroxy, straight or branched, optionally substituted lower alkoxy, -SH, straight or branched, optionally substituted lower alkylthio, nitro, cyano, –NR'R", $-CO_2R'$, -C(O)-NR'R", -N(R'")C(O)-R', -N(R'")-C(O)NR'R", wherein R', R" and R'" each independently represents a hydrogen atom or a straight or branched, optionally substituted lower alkyl group or R' and R" together with the atom to which they are attached form a cyclic group.

Also preferred are compounds of formula (I) as defined above wherein R2 represents an optionally substituted group selected from lower alkyl, lower alkenyl, lower alkynyl, saturated or unsaturated cycloalkyl, phenyl, phenethyl, furan-2-ylmethyl, furan-3-ylmethyl, thiophen-2-ylmethyl, thiophen-3-ylmethyl, pyridyl, and pyridylmethyl or a saturated or unsaturated cycloalkylmethyl group which has at least one substituent and is selected from substituted cyclopropylmethyl, substituted cyclobutylmethyl and substituted cyclopentylmethyl; the substituents of the cyclic groups present in R2 being one, two or three substituents selected from halogen, straight or branched, optionally substituted lower alkyl, hydroxy, straight or branched, optionally substituted lower alkoxy, -SH, straight or branched, optionally substituted lower alkylthio, nitro, cyano, -NR'R", $-CO_2R'$, -C(O)-NR'R", -N(R'")C(O)-R', -N(R'")-C(O)NR'R", wherein R', R" and R'" each independently represents a hydrogen atom or a straight or branched, optionally substituted lower alkyl group or R' and R" together with the atom to which they are attached form a cyclic group.

Preferred compounds of formula (II) according to the invention as defined above are those wherein R1 represents a group selected from phenyl, 2-thienyl, 3-thienyl, thiophen-2-ylmethyl, thiophen-3-ylmethyl, furan-2-ylmethyl or furan-3-ylmethyl, the cyclic groups present in R1 being optionally substituted with one to three

substitutentsubstituents selected from fluorine, chlorine, bromine, methyl, methoxy, trifluoromethyl, ethyl, tert-butyl, hydroxy and cyano.

In particularly preferred embodiments R1 represents a group selected from phenyl, 2-fluorophenyl, 3-flurorophenyl, 4-fluorophenyl, 3-methylphenyl, 4-methylphenyl, 2,5-difluorophenyl, 2,6-difluorophenyl, 2,4,5-trifluorophenyl, 5-methylfuran-2-ylmethyl, 4-fluoro-2-methylphenyl, 3-fluoro-4-methoxyphenyl, 3-methyl-thiophen-2-ylmethyl, 4,5-dimethylthiophen-2-ylmethyl, thiophen-3-ylmethyl, 5-methylfuran-2-ylmethyl, 5-methyl-2-trifluoromethylfuran-3-ylmethyl, and 2,5-dimethylfuran-3-ylmethyl,

Also preferred are compounds of formula (II) as defined above wherein R2 represents a pent-4-enyl, pentyl, butyl, allyl, benzyl, thiophen-2-ylmethyl, thiophen-3-ylmethyl, furan-2-ylmethyl, furan-3-ylmethyl, phenethyl, cyclopentyl, cyclohexyl or cyclohexylmethyl group, the cyclic groups present R2 being optionally substituted with one to three substitutentsubstituents selected from fluorine, chlorine, bromine, methyl, methoxy, trifluoromethyl, ethyl, tert-butyl, hydroxy and cyano.

In particularly preferred embodiments R2 represents a group selected from 3-fluorobenzyl, 2,4,5-trifluorobenzyl, 3,4,5-trifluorobenzyl, 5-bromothiophen-2-ylmethyl, 3,4-dimethoxyphenylethyl, 3-methylthiophen-2-ylmethyl, thiophen-3-ylmethyl, 4-bromo-5-methylthiophen-2-ylmethyl, 4,5-dimethylfuran-2-ylmethyl, furan-3-ylmethyl, 2-fluoro-4-methoxybenzyl, 2-(4-fluorophenyl)ethyl, butyl, pent-4-enyl and cyclopentyl.

Further preferred compounds of formula (II) are those wherein A is –CH2-, m and n are both 0, and B represents a group selected from straight or branched, optionally substituted lower alkyl, hydroxy, straight or branched, optionally substituted lower alkoxy, cyano, nitro, -CH=CR'R", -C(O)OR', -OC(O)R', -SC(O)R', -C(O)NR'R", -NR'C(O)OR", -NR'C(O)NR", cycloalkyl, phenyl, naphthanelyl, 5,6,7,8-tetrahydronaphthanelyl, benzo[1,3]dioxolyl, heteroaryl or heterocyclyl; R' and R" being as defined above; and wherein the cyclic groups represented by B are optionally substituted by one, two or three substitutuents selected from halogen, hydroxy, straight or branched, optionally substituted lower alkyl, phenyl, -OR', -SR', -NR'R", -NHCOR', -CONR'R", -CN, $-NO_2$ and -COOR'; R' and R" being as defined above;

In other embodiments of formula (II) A is –CH2-, B is as defined above and at least one of m or n is not 0.

Also preferred are compounds of formula (II) wherein B represents a thiophen-2-yl group or a phenyl group which is optionally substituted with one to three substituents selected from halogen atoms, or hydroxy, methyl, $-CH_2OH$, -OMe, $-NMe_2$, -NHCOMe, $-CONH_2$, -CN, $-NO_2$, -COOMe, or $-CF_3$ groups. Most preferred are compounds wherein B represents a phenyl, 4-fluorophenyl, 3-hydroxyphenyl or thiophen-2-yl group.

In particularly preferred compounds of formula (II) n= 0 or 1; m is an integer from 1 to 6; and A represents a $-CH_2-$, -CH=CH-, -CO-, -NMe-, -O- or -S- group. Most preferred are compounds wherein m is 1, 2 or 3 and A represents a $-CH_2-$, -CH=CH-, or -O- group.

Preferably, in compounds of formula (II) the sequence $B-(CH_2)_n-A-(CH_2)_m-$ represents a group selected from 3-phenoxypropyl, 2-phenoxyethyl, 3-phenylallyl, phenethyl, 3-phenylpropyl, 3-(3-hydroxyphenoxy)propyl, 3-(4-fluorophenoxy)propyl, 3-thiophen-2-ylpropyl, allyl, heptyl, 3-cyanopropyl and methyl.

X^- represents in the preferred embodiments of formula (II) a chloride, bromide, trifluoroacetate or methanesulphonate anion.

Also preferred are compounds of formula (I) or (II) wherein p is 2 and/or wherein the azabicyclic ring is substituted in the 3-position.

The compounds of the present invention represented by formula (I) and salts thereof such as those represented by formula (II), may have one or more asymmetric atoms. All possible stereoisomers are included, such as compounds of formula (I) or (II) wherein the carbon at the 3-position of the azabicyclic ring has either R or S configuration. All single isomers and mixtures of the isomers fall within the scope of the present invention.

The following compounds of general formula (I) are intended to illustrate the general scope of the present invention.

(3-Fluorobenzyl)-(3-fluorophenyl)carbamic acid (3R)-1-azabicyclo[2.2.2]oct-3-yl ester
m-Tolyl-(2,4,5-trifluorobenzyl)carbamic acid (3R)-1-azabicyclo[2.2.2]oct-3-yl ester
(3-Fluorophenyl)-(3,4,5-trifluorobenzyl)carbamic acid (3R)-1-azabicyclo[2.2.2]oct-3-yl ester
Cyclohexylmethyl-(2-fluorophenyl)carbamic acid (3R)-1-azabicyclo[2.2.2]oct-3-yl ester

[2-(3,4-Dimethoxyphenyl)ethyl]-(5-methylfuran-2-ylmethyl)carbamic acid (3R)-1-azabicyclo[2.2.2]oct-3-yl ester

(5-Bromothiophen-2-ylmethyl)-(2,4,5-trifluorophenyl)carbamic acid (3R)-1-azabicyclo[2.2.2]oct-3-yl ester

(4-Fluoro-2-methylphenyl)-(3-methylthiophen-2-ylmethyl)carbamic acid (3R)-1-azabicyclo[2.2.2]oct-3-yl ester

(3-Fluoro-4-methoxyphenyl)thiophen-3-ylmethylcarbamic acid (3R)-1-azabicyclo[2.2.2]oct-3-yl ester

Thiophen-3-ylmethyl-(2,4,5-trifluorobenzyl)carbamic acid (3R)-1-azabicyclo[2.2.2]oct-3-yl ester

(4-Bromo-5-methylthiophen-2-ylmethyl)-(3-methylthiophen-2-ylmethyl)carbamic acid (3R)-1-azabicyclo[2.2.2]oct-3-yl ester

(4,5-Dimethylfuran-2-ylmethyl)-(5-methylfuran-2-ylmethyl)carbamic acid (3R)-1-azabicyclo[2.2.2]oct-3-yl ester

Furan-3-ylmethyl-(5-methyl-2-trifluoromethylfuran-3-ylmethyl)carbamic acid (3R)-1-azabicyclo[2.2.2]oct-3-yl ester

(2,5-Dimethylfuran-3-ylmethyl)-(2-fluoro-4-methoxybenzyl)carbamic acid (3R)-1-azabicyclo[2.2.2]oct-3-yl ester

[2-(4-Fluorophenyl)ethyl]-(3-methylthiophen-2-ylmethyl)carbamic acid (3R)-1-azabicyclo[2.2.2]oct-3-yl ester

Butyl-(2,5-difluorophenyl)carbamic acid (3R)-1-azabicyclo[2.2.2]oct-3-yl ester

(2,6-Difluorophenyl)pent-4-enylcarbamic acid (3R)-1-aza-bicyclo[2.2.2]oct-3-yl ester

Cyclopentyl-(4,5-dimethylthiophen-2-ylmethyl)carbamic acid (3R)-1-azabicyclo[2.2.2]oct-3-yl ester

Benzylphenylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester

Benzyl(4-fluorophenyl)carbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester

Benzyl-p-tolylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester

Butylphenylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester

Phenylthiophen-2-ylmethylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester

Phenethylphenylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester

Pentylphenylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester

Pent-4-enylphenylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester

Phenylthiophen-3-ylmethylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester

Butylthiophen-2-ylmethylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester

Bis-thiophen-2-ylmethylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester

Furan-2-ylmethyl-2-thiophen-2-ylmethylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester

Allylthiophen-2-ylmethylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester
Cyclopentylthiophen-2-ylmethylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester
Furan-2-ylmethylphenylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester
Bis-furan-2-ylmethylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester
Benzylphenylcarbamic acid 1-azabicyclo[2.2.1]hept-4-yl ester
Benzylphenylcarbamic acid 1-azabicyclo[2.2.2]oct-4-yl ester
and pharmaceutically acceptable salts thereof.

The following salts of general formula (II) are intended to illustrate the general scope of the present invention.

(3R)-3-[(3-Fluorobenzyl)-(3-fluorophenyl)carbamoyloxy]-1-(2-phenoxyethyl)-1-azoniabicyclo[2.2.2]octane bromide
(3R)-3-[(3-Fluorobenzyl)-(3-fluorophenyl)carbamoyloxy]-1-(3-phenylpropyl)-1-azoniabicyclo[2.2.2]octane bromide
(3R)-1-(2-Phenoxyethyl)-3-[m-tolyl-(2,4,5-trifluorobenzyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane bromide
(3R)-1-(3-Phenylpropyl)-3-[m-tolyl-(2,4,5-trifluorobenzyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane bromide
(3R)-3-[(3-Fluorophenyl)-(3,4,5-trifluorobenzyl)carbamoyloxy]-1-(2-phenoxyethyl)-1-azoniabicyclo[2.2.2]octane bromide
(3R)-3-[Cyclohexylmethyl-(2-fluorophenyl)carbamoyloxy]-1-(2-phenoxyethyl)-1-azoniabicyclo[2.2.2]octane bromide
(3R)-3-[Cyclohexylmethyl-(2-fluorophenyl)carbamoyloxy]-1-(3-phenylpropyl)-1-azoniabicyclo[2.2.2]octane bromide
(3R)-1-Allyl-3-[[2-(3,4-dimethoxyphenyl)ethyl]-(5-methylfuran-2-ylmethyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane bromide
(3R)-3-[(5-Bromothiophen-2-ylmethyl)-(2,4,5-trifluorophenyl)carbamoyloxy]-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane trifluoroacetate
(3R)-3-[[2-(3,4-dimethoxyphenyl)ethyl]-(5-methylfuran-2-ylmethyl)carbamoyloxy]-1-(4-ethoxycarbonylbutyl)-1-azoniabicyclo[2.2.2]octane trifluoroacetate
(3R)-3-[(4-Fluoro-2-methylphenyl)-(3-methylthiophen-2-ylmethyl)carbamoyloxy]-1-(2-phenoxyethyl)-1-azoniabicyclo[2.2.2]octane trifluoroacetate
(3R)-3-[(3-Fluoro-4-methoxyphenyl)thiophen-3-ylmethylcarbamoyloxy]-1-(3-phenylallyl)-1-azoniabicyclo[2.2.2]octane trifluoroacetate
(3R)-1-Phenethyl-3-[thiophen-3-ylmethyl-(2,4,5-trifluorobenzyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane trifluoroacetate

(3R)-3-[(4-Bromo-5-methylthiophen-2-ylmethyl)-(3-methylthiophen-2-ylmethyl)carbamoyloxy]-1-(3-phenylpropyl)-1-azoniabicyclo[2.2.2]octane trifluoroacetate

(3R)-3-[(4,5-Dimethylfuran-2-ylmethyl)-(5-methylfuran-2-ylmethyl)carbamoyloxy]-1-[3-(3-hydroxyphenoxy)propyl]-1-azoniabicyclo[2.2.2]octane trifluoroacetate

(3R)-1-[3-(4-Fluorophenoxy)propyl]-3-[furan-3-ylmethyl-(5-methyl-2-trifluoromethylfuran-3-ylmethyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane trifluoroacetate

(3R)-3-[(2,5-Dimethylfuran-3-ylmethyl)-(2-fluoro-4-methoxybenzyl)carbamoyloxy]-1-(3-thiophen-2-ylpropyl)-1-azoniabicyclo[2.2.2]octane trifluoroacetate

(3R)-1-Allyl-3-[2-(4-fluorophenyl)ethyl]-(3-methylthiophen-2-ylmethyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane trifluoroacetate

(3R)-3-[Butyl-(2,5-difluorophenyl)carbamoyloxy]-1-heptyl-1-azoniabicyclo[2.2.2]octane trifluoroacetate

(3R)-1-(3-cyanopropyl)-3-[(2,6-difluorophenyl)pent-4-enylcarbamoyloxy]-1-azoniabicyclo[2.2.2]octane trifluoroacetate

(3R)-3-[Cyclopentyl-(4,5-dimethylthiophen-2-ylmethyl)carbamoyloxy]-1-methyl-1-azoniabicyclo[2.2.2]octane trifluoroacetate

3-(R)(Benzylphenylcarbamoyloxy)-1-(3-phenylallyl)-1-azoniabicyclo[2.2.2]octane bromide

1-Allyl-3-(R)(benzylphenylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane bromide

3-(R)(Benzylphenylcarbamoyloxy)-1-phenethyl-1-azoniabicyclo[2.2.2]octane bromide

3-(R)(Benzylphenylcarbamoyloxy)-1-(3-thiophen-2-ylpropyl)-1-azoniabicyclo[2.2.2]-octane bromide

3-(R)(Benzylphenylcarbamoyloxy)-1-(3-phenylpropyl)-1-azoniabicyclo[2.2.2]octane bromide

3-(R)(Benzylphenylcarbamoyloxy)-1-(2-phenoxyethyl)-1-azoniabicyclo[2.2.2]octane bromide

3-(R)(Butylphenylcarbamoyloxy)-1-(3-phenylallyl)-1-azoniabicyclo[2.2.2]octane bromide

1-Allyl-3-(R)(butylphenylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane bromide

3-(R)(Butylphenylcarbamoyloxy)-1-(2-phenoxyethyl)-1-azoniabicyclo[2.2.2]octane bromide

3-(R)(Butylphenylcarbamoyloxy)-1-[3-(3-hydroxyphenoxy)propyl]-1-azoniabicyclo [2.2.2]octane bromide

3-(R)(Butylphenylcarbamoyloxy)-1-[3-(4-fluorophenoxy)propyl]-1-azoniabicyclo[2.2.2] octane bromide

3-(R)(Butylphenylcarbamoyloxy)-1-(3-thiophen-2-ylpropyl)-1-azoniabicyclo[2.2.2]octane bromide

3-(R)(Butylphenylcarbamoyloxy)-1-(3-phenylpropyl)-1-azoniabicyclo[2.2.2]octane bromide

3-(R)(Phenylthiophen-2-ylmethylcarbamoyloxy)-1-(3-thiophen-2-ylpropyl)-1-azoniabicyclo[2.2.2]octane bromide

1-(2-Phenoxyethyl)-3-(R)-(phenylthiophen-2-ylmethylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane bromide

1-Allyl-3-(R)(phenylthiophen-2-ylmethylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane bromide

3-(R)(Phenethylphenylcarbamoyloxy)-1-(2-phenoxyethyl)-1-azoniabicyclo[2.2.2]octane trifluoroacetate

1-Heptyl-3-(R)(pent-4-enylphenylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane trifluoroacetate

1-Allyl-3-(R)-(phenylthiophen-3-ylmethylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane trifluoroacetate

3-(R)(phenylthiophen-3-ylmethylcarbamoyloxy)-1-(3-thiophen-2-ylpropyl)-1-azoniabicyclo[2.2.2]octane bromide

1-(2-Phenoxyethyl)-3-(R)(phenylthiophen-3-ylmethylcarbamoyloxy)-1-azoniabicyclo-[2.2.2]octane bromide

3-(R)(Bis-thiophen-2-ylmethylcarbamoyloxy)-1-(3-phenylpropyl)-1-azoniabicyclo-[2.2.2]octane bromide

3-(R)(Bis-thiophen-2-ylmethylcarbamoyloxy)-1-(3-thiophen-2-ylpropyl)-1-azoniabicyclo-[2,2.2]octane bromide

1-Allyl-3-(R)(allylthiophen-2-ylmethylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane trifluoroacetate

3-(R)(Cyclopentylthiophen-2-ylmethylcarbamoyloxy)-1-(3-phenylpropyl)-1-azoniabicyclo[2.2.2]octane trifluoroacetate

3-(R)(Furan-2-ylmethylphenylcarbamoyloxy)-1-(3-phenylpropyl)-1-azoniabicyclo-[2.2.2]octane trifluoroacetate

1-Allyl-3-(R)(bis-furan-2-ylmethylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane trifluoroacetate.

Particularly preferred individual compounds of formula (I) include:

[2-(3,4-Dimethoxyphenyl)ethyl]-(5-methylfuran-2-ylmethyl)carbamic acid (3R)-1-azabicyclo[2.2.2]oct-3-yl ester

(5-Bromothiophen-2-ylmethyl)-(2,4,5-trifluorophenyl)carbamic acid (3R)-1-azabicyclo[2.2.2]oct-3-yl ester

(4-Fluoro-2-methylphenyl)-(3-methylthiophen-2-ylmethyl)carbamic acid (3R)-1-azabicyclo[2.2.2]oct-3-yl ester

(3-Fluoro-4-methoxyphenyl)thiophen-3-ylmethylcarbamic acid (3R)-1-azabicyclo[2.2.2]oct-3-yl ester

Thiophen-3-ylmethyl-(2,4,5-trifluorobenzyl)carbamic acid (3R)-1-azabicyclo[2.2.2]oct-3-yl ester

(4-Bromo-5-methylthiophen-2-ylmethyl)-(3-methylthiophen-2-ylmethyl)carbamic acid (3R)-1-azabicyclo[2.2.2]oct-3-yl ester

(4,5-Dimethylfuran-2-ylmethyl)-(5-methylfuran-2-ylmethyl)carbamic acid (3R)-1-azabicyclo[2.2.2]oct-3-yl ester

Furan-3-ylmethyl-(5-methyl-2-trifluoromethylfuran-3-ylmethyl)carbamic acid (3R)-1-azabicyclo[2.2.2]oct-3-yl ester

(2,5-Dimethylfuran-3-ylmethyl)-(2-fluoro-4-methoxybenzyl)carbamic acid (3R)-1-azabicyclo[2.2.2]oct-3-yl ester

[2-(4-Fluorophenyl)ethyl]-(3-methylthiophen-2-ylmethyl)carbamic acid (3R)-1-azabicyclo[2.2.2]oct-3-yl ester

Butyl-(2,5-difluorophenyl)carbamic acid (3R)-1-azabicyclo[2.2.2]oct-3-yl ester

(2,6-Difluorophenyl)pent-4-enylcarbamic acid (3R)-1-azabicyclo[2.2.2]oct-3-yl ester

Cyclopentyl-(4,5-dimethylthiophen-2-ylmethyl)carbamic acid (3R)-1-azabicyclo[2.2.2]oct-3-yl ester.

Particularly preferred individual compounds of formula (II) include:

(3R)-3-[(3-Fluorobenzyl)-(3-fluorophenyl)carbamoyloxy]-1-(2-phenoxyethyl)-1-azoniabicyclo[2.2.2]octane bromide

(3R)-3-[(3-Fluorobenzyl)-(3-fluorophenyl)carbamoyloxy]-1-(3-phenylpropyl)-1-azoniabicyclo[2.2.2]octane bromide

(3R)-1-(2-Phenoxyethyl)-3-[m-tolyl-(2,4,5-trifluorobenzyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane bromide

(3R)-1-(3-Phenylpropyl)-3-[m-tolyl-(2,4,5-trifluorobenzyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane bromide

(3R)-3-[(3-Fluorophenyl)-(3,4,5-trifluorobenzyl)carbamoyloxy]-1-(2-phenoxyethyl)-1-azoniabicyclo[2.2.2]octane bromide

(3R)-1-Allyl-3-[[2-(3,4-dimethoxyphenyl)ethyl]-(5-methylfuran-2-ylmethyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane bromide

(3R)-3-[(5-Bromothiophen-2-ylmethyl)-(2,4,5-trifluorophenyl)carbamoyloxy]-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane trifluoroacetate

(3R)-3-[[2-(3,4-dimethoxyphenyl)ethyl]-(5-methylfuran-2-ylmethyl)carbamoyloxy]-1-(4-ethoxycarbonylbutyl)-1-azoniabicyclo[2.2.2]octane trifluoroacetate

(3R)-3-[(4-Fluoro-2-methylphenyl)-(3-methylthiophen-2-ylmethyl)carbamoyloxy]-1-(2-phenoxyethyl)-1-azoniabicyclo[2.2.2]octane trifluoroacetate

(3R)-3-[(3-Fluoro-4-methoxyphenyl)thiophen-3-ylmethylcarbamoyloxy]-1-(3-phenylallyl)-1-azoniabicyclo[2.2.2]octane trifluoroacetate

(3R)-1-Phenethyl-3-[thiophen-3-ylmethyl-(2,4,5-trifluorobenzyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane trifluoroacetate

(3R)-3-[(4-Bromo-5-methylthiophen-2-ylmethyl)-(3-methylthiophen-2-ylmethyl)carbamoyloxy]-1-(3-phenylpropyl)-1-azoniabicyclo[2.2.2]octane trifluoroacetate

(3R)-3-[(4,5-Dimethylfuran-2-ylmethyl)-(5-methylfuran-2-ylmethyl)carbamoyloxy]-1-[3-(3-hydroxyphenoxy)propyl]-1-azoniabicyclo[2.2.2]octane trifluoroacetate

(3R)-1-[3-(4-Fluorophenoxy)propyl]-3-[furan-3-ylmethyl-(5-methyl-2-trifluoromethylfuran-3-ylmethyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane trifluoroacetate

(3R)-3-[(2,5-Dimethylfuran-3-ylmethyl)-(2-fluoro-4-methoxybenzyl)carbamoyloxy]-1-(3-thiophen-2-ylpropyl)-1-azoniabicyclo[2.2.2]octane trifluoroacetate

(3R)-1-Allyl-3-[2-(4-fluorophenyl)ethyl]-(3-methylthiophen-2-ylmethyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane trifluoroacetate

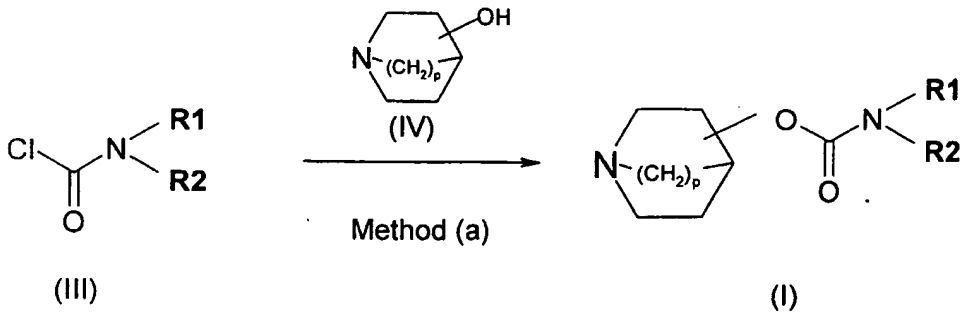
(3R)-3-[Butyl-(2,5-difluorophenyl)carbamoyloxy]-1-heptyl-1-azoniabicyclo[2.2.2]octane trifluoroacetate

(3R)-1-(3-Cyanopropyl)-3-[(2,6-difluorophenyl)pent-4-enylcarbamoyloxy]-1-azoniabicyclo[2.2.2]octane trifluoroacetate

(3R)-3-[Cyclopentyl-(4,5-dimethylthiophen-2-ylmethyl)carbamoyloxy]-1-methyl-1-azoniabicyclo[2.2.2]octane trifluoroacetate.

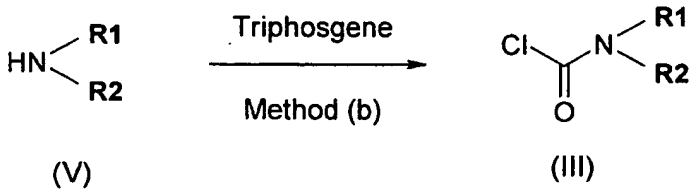
The present invention also provides processes for preparing compounds of formulas (I) and (II).

Compounds of general formula (I) may be prepared by method (a) illustrated in the following scheme and detailed in the experimental section.



In formulas (I), (III) and (IV), R1, R2 and p are as defined above.

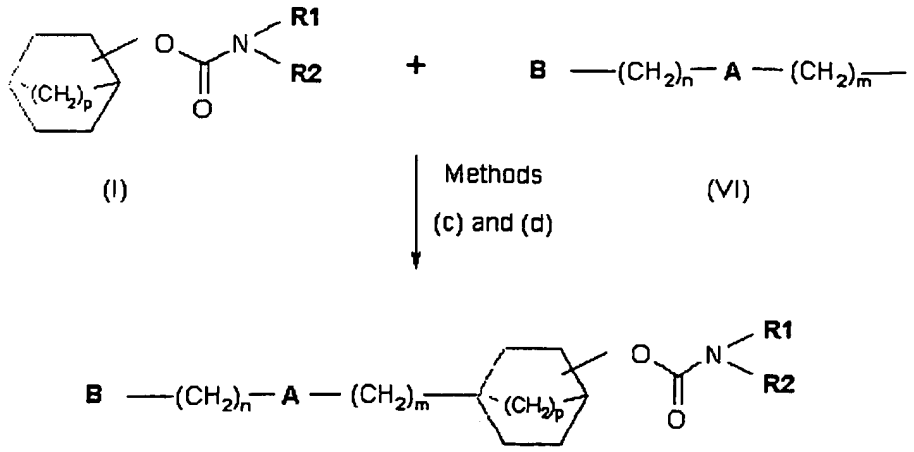
Compounds of general formula (III) may be prepared from the corresponding secondary amines following the standard method (b) described in literature.



Amines of general formula (V) that are not commercially available may be prepared by synthesis according to standard methods, such as alkylation of anilines or reductive alkylation. For example, amines wherein R1 is a substituted thiophen-2-ylmethyl or a substituted furan-2-ylmethyl and R2 is as defined above, may be obtained by reductive alkylation. The corresponding aldehyde is treated with the corresponding primary amine to form the imine, which is reduced with sodium borohydride in MeOH to obtain the secondary amine.

The carbamates of formula (I) may be converted to pharmaceutically acceptable salts by methods known in the art. Typically, a carbamate of formula (I) is treated with an inorganic or organic acid such as fumaric, tartaric, succinic or hydrochloric acid.

The quaternary ammonium derivatives of general formula (II), may be prepared by reaction of an alkylating agent of general formula (VI) with compounds of general formula (I), as described in the following scheme. In formulas (I), (II) and (VI), R1, R2, A, B, X, n, m and p are as defined above.

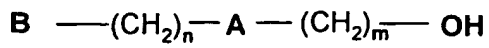


(II)

In formula (VI), W represents any suitable leaving group, such as a group X as defined above. Preferably, W represents a group X.

This alkylation reaction may be carried out by two different experimental procedures, (c) and (d) which are described in the experimental section below. In particular method (d) provides a new experimental process, using solid phase extraction methodologies that allow the parallel preparation of several compounds. If W represents a group other than X, the quaternary ammonium salt of formula (II) is produced from the product of method (c) or (b) by carrying out an exchange reaction according to standard methods that replace the anion W^- with the desired anion X^-.

Methods (c) and (d) are described in the experimental section. Compounds of general formula (VI) which are not commercially available have been prepared by synthesis according to standard methods. For example, compounds wherein n = 0 and A= -O-, -S- or –NR4, wherein R4 is as defined above, were obtained by reaction of the corresponding aromatic derivative or its potassium salt with an alkylating agent of general formula Y-(CH_2)m-X, wherein X may be a halogen and Y may be a halogen or a sulphonate ester. In other examples, compounds of general formula (VI), where n>=1 were synthesisesynthesized from the corresponding alcohol derivative of general formula (VII) by known methods.



(VII)

Compounds of formula (IV) could be:

4-hydroxy-1-azabicyclo[2.2.1]heptane, described in WO150080

4-hydroxy-1-azabicyclo[2.2.2]octane, described in Grob, C.A. et.al. Helv.Chim.Acta (1958), 41, 1184-1190

(3R)-3-hydroxy-1-azabicyclo[2.2.2]octane or (3S)-3-hydroxy-1-azabicyclo[2.2.2]octane, described in Ringdahl, R. Acta Pharm Suec. (1979), 16, 281-283 and commercially available from CU Chemie Uetikon GmbH.

The structures of the prepared compounds were confirmed by ^{1}H-NMR and MS. The NMR were recorded using a Varian 300 MHz instrument and chemical shifts are expressed as parts per million (δ) from the internal reference tetramethyl silane. Their purity was determined by HPLC, using reverse phase chromatography on a Waters instrument, obtaining values above 95%. Molecular ions were obtained by electrospray ionization mass spectrometry on a Hewlett Packard instrument.

HPLC-MS experiments were performed on a Gilson instrument equipped with a binary pump (Gilson 321); a vacuum degasser (Gilson 864); an injector-fraction collector (Gilson 215); two injection modules, analytical and preparative (Gilson 819); a valve (Gilson Valvemate 7000); a 1/1000 splitter (Acurate by LC Packings); a make-up pump (Gilson 307); a diode array detector (Gilson 170) and an MS detector (a Thermoquest Finnigan aQa quadrupole, a mass spectrometer with ES and APCI ionization modes). The HPLC-MS was controlled by an IBM PC.

Method (a)

Preparation of butylphenylcarbamic acid (3R)-1-azabicyclo[2.2.2]oct-3-yl ester.

0.65 g (28.50 mmol) of sodium was added to 70 ml of dry toluene. The suspension was refluxed with vigorous stirring. When all the sodium was melted, 3.60 g (28.30 mmol) of (3R)-3-hydroxy-1-azabicyclo[2.2.2]octane was added and stirring continued for 2 hours, by which time all the sodium had reacted to form the alcoholate. 6.00 g (28.30 mmol) of phenylbutylcarbamyl chloride (Intermediate I-1) dissolved in 30 ml of toluene was then slowly added. The mixture was refluxed for one hour, and then the reaction was stirred overnight at room temperature. The suspension was filtered and the filtrate evaporated. Ether was added to the residue and stirred for 10 min. The suspension was filtered and the filtrate concentrated in vacuo to obtain 7.18 g of brown oil. This product was purified by column chromatography (silica gel, chloroform/ethanol/ammonia 140:8:1) to yield 1.78 g (5.89 mmol) (22%) of a pure product, structure confirmed by ^{1}H-NMR.

^{1}H-NMR (300 MHz,CDCl3): δ 0.9 (m, 3H), 1.3 (m, 4H), 1.5 (m, 4H), 1.9 (s, 1H), 2.7 (m, 5H), 3.2 (m, 1H), 3.7 (m, 2H), 4.7 (m, 1H), 7.2-7.4 (m, 5H); MS $[M+1]^+$: 303.

Preparation of cyclopentylthiophen-2-ylmethylcarbamic acid (3R)-1-azabicyclo[2.2.2]oct-3-yl ester.

0.57 g (24.59 mmol) of sodium was added to 70 ml of dry toluene. The suspension was refluxed with vigorous stirring. When all the sodium was melted, 3.11 g (24.42 mmol) of (3R)-3-hydroxy-1-azabicyclo[2.2.2]octane was added and stirred for 2 hours, by which time all the sodium had reacted to form the alcoholate. 4.96 g (20.35 mmol) of cyclopentylthiophen-2-ylmethylcarbamyl chloride (Intermediate I-2) dissolved in 30 ml of toluene was then slowly added. The mixture was refluxed for five hours, and then the reaction was stirred overnight at room temperature. The suspension was filtered and the filtrate washed with water. The organic layer was extracted with 20 % HCl and the aqueous layer basified with 8N NaOH and extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous Na_2SO_4 and evaporated. The oil obtained (4.50 g) was purified by column chromatography (silica gel, chloroform/ethanol/ammonia 225:8:1) to obtain 2.25 g (6.73 mmol) (33%) of a pure product, structure confirmed by ^{1}H-NMR.

1H-NMR (300 MHz, DMSO-d_6): δ 1.20-1.40 (m, 1H), 1.45-1.72 (m, 11H), 1.89 (bs, 1H), 2.45-2.62 (m, 5H), 3.03-3.10 (m, 1H), 4.22 (bs, 1H), 4.50-4.63 (m, 3H), 6.93-6.99 (m, 2H), 7.38 (m, 1H).; MS $[M+1]^+$: 335.

Preparation of benzylphenylcarbamic acid 1-azabicyclo[2.2.1]hept-4-yl ester

In a flask under nitrogen, 3 ml of THF and 150 mg (1.33 mmolesmmol) of 4-hydroxy-1-azabicyclo[2.2.1]heptane were placed. The suspension was cooled to –60°C and 0.7 ml (1.46 mmolesmmol) of LDA was added dropwise. After the addition the temperature was allowed to rise to 0°C and was maintained for two hours. A solution of 295 mg (1.20 mmolesmmol) of benzylphenylcarbamyl chloride in 2 ml of THF was added in 30 minutes. The reaction mixture was allowed to warm to room temperature and stirred for 18 hours. The suspension was filtered and the filtrate concentrated in vacuo. The residue obtained was extracted with dichloromethane and water. The organic phase was extracted with 2N HCl and the aqueous phase basified with 8N NaOH and extracted with dichloromethane. The organic phases were combined, dried over anhydrous Na_2SO_4 and evaporated. The oil obtained (162 mg) was purified by HPLC-MS to obtain 4.86 mg (0.015 mmolesmmol) 1.3% of a pure product as a formate, structure confirmed by ^{1}H-NMR.

1H-NMR (300 MHz, DMSO-d_6) : δ 1.86 (m, 4H), 2.65 (s, 2H), 2.77 (bs, 2H), 3.03 (bs, 2H), 4.84 (s, 2H), 7.14-7.32 (m, 10H). 8.19 (s, 1H); MS $[M\text{-}HCOO]^+$: 323.

m-Tolyl-(2,4,5-trifluorobenzyl)carbamic acid (3R)-1-azabicyclo[2.2.2]oct-3-yl ester

0.69 g (30 mmol) of sodium (in small portions) were added to 140 ml of dry toluene and the suspension was refluxed with vigorous stirring. When all the sodium was melted, 3.78 g (29.73 mmol) of (3R)-3-hydroxy-1-azabicyclo[2.2.2]octane were added in five portions, and the suspension obtained was refluxed for 2 hours, by which time all the sodium had reacted to form the alcoholate. A solution of 8.11 g (25.85 mmol) of m-tolyl-(2,4,5-trifluorobenzyl)carbamyl chloride (Intermediate I-3) in 60 ml of toluene was then slowly added. The mixture obtained was refluxed with stirring at room temperature for 64 more hours. After this time, the reaction mixture was filtered and the solution obtained was extracted with HCl 2N (2 x 125 ml). The aqueous layers were combined, basified with solid K_2CO_3 and extracted with $CHCl_3$. The organic layer was dried over anhydrous $MgSO_4$, filtered and evaporated. The oil obtained (6.30 g) was purified by column chromatography (silica gel, chloroform/ethanol 5:1) to obtain 3.05 g (29.2%) of a pure product as an oil, structure confirmed by ^{1}H-NMR.

^{1}H-NMR ($CDCl_3$): δ 1.22-1.40 (m, 1H), 1.40-1.60 (m, 2H), 1.60-1.75 (m, 1H), 2.0 (m, 1H), 2.32 (s, 3H), 2.60-2.90 (m, 5H), 3.17-3.26 (m, 1H), 4.78-4.83 (m, 1H), 4.86 (s, 2H), 6.82-7.0 (m, 3H), 7.03-7.07 (m, 1H), 7.15-7.25 (m, 2H).

MS $[M+1]^+$: 405

Method (b)

Carbamyl chlorides of general formula (III) were prepared according to procedures described in the literature: M. Saraswati et al. Drug Development Research (1994), 31, 142-146; G. M. Shutske et al. J. Heterocycl. Chem. (1990), 27, 1617; GB 1246606; US 2762796.

Intermediate I-1 – Preparation of butylphenylcarbamyl chloride.

To a solution of 6.72 g (45 mmol) of butylphenylamine in 50 ml of methylene chloride cooled to 10°C was added slowly with stirring 6.67 g (22.5 mmol) of triphosgene in 40 ml of methylene chloride. The reaction was allowed to continue at room temperature for 27 hours. The solvent was evaporated and the residue extracted twice with n-hexane. The organic solution was concentrated in vacuo to yield 9.11g (43.03 mmol) of a yellow

oil (96%). ^{1}H-NMR ($CDCl_3$) : δ 0.9 (m, 3H), 1.3 (m, 2H), 1.6 (m, 2H), 3.7 (m, 2H), 7.2-7.4 (m, 5H).

Intermediate I-2 – Preparation of cyclopentylthiophen-2-ylmethylcarbamyl chloride

To a solution of 5.0 g (27.58 mmol) of cyclopentylthiophen-2-ylmethylamine in 40 ml of methylene chloride at 10°C was added slowly with stirring 4.09 g (13.79 mmol) of triphosgene in 35 ml of methylene chloride. The reaction was allowed to continue at room temperature for 64 hours, refluxed for 4 hours and continued for 25 hours more at room temperature. The solvent was evaporated and the residue extracted with n-hexane. The organic solution was concentrated to yield 4.96 g (20.34 mmol) of a brown oil (74%). ^{1}H-NMR ($CDCl_3$) : δ 1.4 (m, 8H), 4.2 (bs, 1H), 4.5 (m, 2H), 6.8-7.3 (m, 3H).

Intermediate I-3 – Preparation of m-tolyl-(2,4,5-trifluorobenzyl)carbamyl chloride

To a solution of 6.5 g (25.87 mmol) of m-tolyl-(2,4,5-trifluorobenzyl)amine (prepared from 2,4,5-trifluorobenzaldehyde and m-tolylamine by reductive alkylation) in 45 ml of methylene chloride, cooled to -10°C, was added slowly with stirring a solution of 3.84 g (12.94 mmol) of triphosgene in 25 ml of methylene chloride. The reaction was brought to room temperature, stirred for 2 hours at this temperature and then refluxed for 10 hours. After this time the solid formed during the process was dissolved. The solvent was evaporated and the residue treated with n-hexane at –25°C. The soluble part was separated and filtered. The filtrate was concentrated in vacuo to yield 8.2 g of the final product in the form of an oil . The structure was confirmed by ^{1}H-NMR.
^{1}H-NMR ($CDCl_3$) : δ 2.30 (s, 3H), 4.85 (s, 2H), 6.70-7.10 (m, 3H), 7.10-7.40 (m, 3H).

Intermediate I-4 – Preparation of [2-(3,4-dimethoxyphenyl)ethyl]-(5-methylfuran-2-ylmethyl)amine

To a solution of 4.82 g (26.6 mmol) of 2-(3,4-dimethoxyphenyl)ethylamine and 3.0 g (27.2 mmol) of 5-methylfuran-2-carbaldehyde in 65 ml of EtOH, 18.3 g of molecular sieves (0.3 nm) were added and the mixture was refluxed for 4 hours. After this time the reaction mixture was cooled to room temperature and filtered . The solution obtained was concentrated in vacuo to obtain an oil. This oil was dissolved in 65 ml of MeOH and 1.01 g (26.6 mmol) of $NaBH_4$ were added in small portions, maintaining the temperature of the reaction at room temperature. The mixture was stirred at this temperature for 16 hours more. After this time the solvent was evaporated in vacuo and the residue was treated with 150 ml of water and extracted twice with ether. The

organic phases were combined, washed with brine, dried over anhydrous $MgSO_4$, filtered and evaporated to dryness to give 6.05 g (82.6%) of the title product as an oil.
MS $[M+1]^+$: 276
^{1}H-NMR ($CDCl_3$) : δ 2.25 (s, 3H), 2.70-2.95 (m, 4H), 3.75 (s, 2H), 3.85 (two singlets, 6H), 5.85 (m, 1H), 6.02 (m, 1H), 6.70-6.85 (m, 3H).

Intermediate I-5 – Preparation of (5-bromothiophen-2-ylmethyl)-(2,4,5-trifluorophenyl)amine

To a solution of 2 g (13.6 mmol) of 2,4,5-trifluorophenylamine and 2.66 g (13.9 mmol) of 5-bromothiophene-2-carbaldehyde in 30 ml of EtOH, 9.4 g of molecular sieves (0.3 nm) were added and the mixture was refluxed for 20 hours. After this time the reaction mixture was cooled to room temperature, filtered and the solvent was evaporated in vacuo. The oil obtained was dissolved in 30 ml of MeOH and 0.51 g (13.6 mmol) of $NaBH_4$ were added in small portions, maintaining the temperature of the reaction at room temperature. The mixture was stirred at this temperature for 20 more hours. After this time the solvent was evaporated in vacuo and the residue was treated with 100 ml of water and extracted twice with ether. The organic phases were combined, washed with brine, dried over anhydrous $MgSO_4$, filtered and evaporated to dryness to give 3.2 g of an oil. This 3.2 g were combined with 3.5 g obtained in a subsequent preparation and the total product obtained (6.7 g) was purified by chromatography on silica gel using a mixture of hexane/AcOEt 5:1→ 1:1 as eluent. Various fractions were combined to give 0.95 g of the title product as an oil. (global yield 8.2%).
MS $[M+1]^+$: 321.323
^{1}H-NMR ($CDCl_3$) : δ 4.10 (bs, NH, 1H), 4.40 (s, 2H), 6.40-6.65 (m, 1H), 6.75-7.10 (m, 3H).

Method (c)

Preparation of (3R)-3-(bis-thiophen-2-ylmethylcarbamoyloxy)-1-(3-thiophen-2-ylpropyl)-1-azoniabicyclo[2.2.2]octane bromide.

0.54 g (1.5 mmol) of bis-thiophen-2-ylmethylcarbamic acid (3R)-1-azabicyclo[2.2.2]oct-3-yl ester, 7.5 ml of tetrahydrofuran and 0.46 g (2.25 mmol) of 2-(3-bromopropyl)thiophene were mixed. The solution was refluxed for 4 hours and stirred at room temperature for 116 hours. Ether was added and the suspension was stirred for 30 min. The solvent was extracted and more ether was added. This procedure was repeated several times in order to eliminate the alkylating agent. Finally the suspension

was filtered and the residue dried in the vacuum oven. The yield was 0.69 g (1.22 mmol) (81%).

^{1}H-NMR (DMSO) : δ 1.78-2.10 (m, 6H), 2.34 (bs, 1H), 2.82 (m, 2H), 3.21-3.46 (m, 7H), 3.89 (m, 1H), 4.54 (m, 4H), 5.06 (m, 1H), 6.95-7.01 (m, 4H), 7.07-7.11 (m, 2H), 7.38-7.49 (m, 3H); MS [M-Br]$^+$: 487; mp : 143°C.

Preparation of (3R)-1-(2-phenoxyethyl)-3-[m-tolyl-(2,4,5-trifluorobenzyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane bromide

0.300 g (0.742 mmol) of m-tolyl-(2,4,5-trifluorobenzyl)carbamic acid (3R)-1-azabicyclo[2.2.2]oct-3-yl ester, 7.0 ml of tetrahydrofuran and 0.253 g (1.258 mmol) of (2-bromoethoxy)benzene were mixed. The solution was refluxed for 55 hours and stirred at room temperature for 16 more hours. After this time the solvent was evaporated in vacuo. Ether was added and the mixture stirred to obtain a solid. This solid was treated with ether several times in order to eliminate the residual alkylating agent. Finally the suspension was filtered and the solid obtained washed with ether and dried. The yield was 0.34 g (75.5%).

m.p.: 137.3-139.1°C

MS [M-Br] $^+$: 525

^{1}H-NMR(DMSO-d_6): δ 1.40-1.70 (m, 1H), 1.70-2.05 (m, 3H), 2.20 (m, 1H), 2.25 (s, 3H), 3.25-3.40 (m, 1H), 3.40-3.80 (m, 6H), 3.95-4.10 (m, 1H), 4.44 (m, 2H), 4.90 (m, 2H), 5.01 (m, 1H), 6.95-7.30 (m, 7H), 7.30-7.60 (m, 4H).

Preparation of (3R)-1-Allyl-3-[[2-(3,4-dimethoxyphenyl)ethyl]-(5-methylfuran-2-ylmethyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane bromide

0.300 g (0.7 mmol) of [2-(3,4-dimethoxyphenyl)ethyl]-(5-methylfuran-2-ylmethyl)carbamic acid (3R)-1-azabicyclo[2.2.2]oct-3-yl ester (Example 12) were dissolved in 5 ml of $CHCl_3$ and 3.5 ml of acetonitrile. To this solution 0.30 ml (0.423 g, 3.5 mmol) of allyl bromide were added and the mixture was stirred for 21 hours at room temperature under N_2 atmosphere. Solvents were evaporated. The residue was treated with ether several times to obtain an oil, which was redissolved in $CHCl_3$ and evaporated to dryness to give 0.365 g (94.8 %) of the title product.

MS [M-Br] $^+$: 469

Method (d)

Preparation of (3R)-1-heptyl-3-(phenylthiophen-3-ylmethylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane trifluoroacetate

30 mg (0.08 mmol) of phenylthiophen-3-ylmethyl carbamic acid (3R)-1-aza-bicyclo[2.2.2]oct-3-yl ester were dissolved in 1ml of DMSO. To this solution 75 mg (0.40 mmol) of heptyl bromide were added. After stirring overnight at room temperature, the mixture was purified by solid phase extraction with a cation exchange Mega Bond Elut cartridge, previously conditioned at pH = 7.5 with 0.1 M NaH_2PO_4 buffer. The reaction mixture was applied to the cartridge and washed first with 2 ml of DMSO and then three times with 5 ml of CH_3CN, rinsing away all starting materials. The ammonium derivative was eluted with 5 ml of 0.03 M TFA solution in CH_3CN:$CHCl_3$ (2:1). This solution was neutralized with 300 mg of poly(4-vinylpyridine), filtered and evaporated to dryness.

The yield was 12 mg (34%) of title compound. ^{1}H- NMR (DMSO-d_6): δ 0.88 (m, 3H), 1.28 (m, 8H), 1.60-2.19 (m, 7H), 3.00-3.41 (m, 7H), 3.83 (m, 1H), 4.88 (s, 2H), 5.99 (m, 1H), 7.01 (m, 1H), 7.21-7.39 (m, 6H), 7.49-7.52 (m, 1H); MS $[M\text{-}CF_3COO]^+$: 441

Also included within the scope of the present invention are pharmaceutical compositions which comprise, as the active ingredient, at least one quinuclidine derivative of general formula (I) or (II) in association with a pharmaceutically acceptable carrier or diluent. Preferably the composition is made up in a form suitable for oral administration.

The pharmaceutically acceptable carriers or diluents which are mixed with the active compound or compounds, to form the composition of this invention are well-known *per se* and the actual excipients used depend *inter alia* on the intended method of administration of the composition.

Compositions of this invention are preferably adapted for oral administration. In this case, the composition for oral administration may take the form of tablets, film-coated tablets, liquid inhalant, powder inhalant and inhalation aerosol; all containing one or more compounds of the invention; such preparations may be made by methods well-known in the art.

The diluents which may be used in the preparation of the compositions include those liquid and solid diluents which are compatible with the active ingredient, together with colouring or flavouring agents, if desired. Tablets or film-coated tablets may conveniently contain between 0.1 mg and 500 mg, preferably from 0.5 to 200 mg of active ingredient. The inhalant compositions may contain between 1μg and 1,000 μg, preferably from 10 to 800 μg of active ingredient. In human therapy, the dose of the compound of general formula (I) or (II) will depend on the desired effect and duration of treatment; adult doses are generally between 0.5 mg and 300 mg per day as tablets and 10 μg and 800 μg per day as inhalant composition.

The components of the present invention, or pharmaceutical compositions containing them, may be used together with a β_2 agonist, steroid, antiallergic drug and/or phosphodiesterase IV inhibitor, for simultaneous, separate or sequential use in the treatment of a respiratory disease.

Pharmacological Action

The following examples demonstrate the excellent pharmacological activities of the compounds of the present invention. The results from human muscarinic receptor binding and in the test on bronchospasm in guinea pigs, were obtained as described below.

Human muscarinic receptor studies.

The binding of [^{3}H]-NMS to human muscarinic receptors was performed according to Waelbroeck et al (1990), Mol. Pharmacol., 38: 267-273. Assays were carried out at 25°C. Membrane preparations from stably transfected Chinese hamster ovary-K1 cells (CHO) expressing the genes for the human muscarinic M3 receptors were used.

For determination of IC_{50}, membrane preparations were suspended in DPBS to a final concentration of 89 μg/ml for the M3 subtype. The membrane suspension was incubated with the tritiated compound for 60 min. After incubation the membrane fraction was separated by filtration and the bound radioactivity determined. Non specific binding was determined by addition of 10^{-4} M atropine. At least six concentrations were assayed in duplicate to generate individual displacement curves.

Our results show that the compounds of the present invention have high affinities for M3 receptors. Preferred compounds of the invention have an IC_{50} (nM) value for muscarinic M3 receptors of less than 35 nM, most preferably less than 10 nM.

The preferred compounds of the invention also show high selectivity for M3 receptors with respect to M2 receptors. Thus, the ratio IC_{50} M2 / IC_{50} M3 is higher than 5, preferably higher than 10, most preferably higher than 15.

Test on bronchospasm in guinea pigs

The studies were performed according to Konzett and Rössler (1940), Arch. Exp. Path. Pharmacol. 195, 71-74. Aqueous solutions of the agents to be tested were nebulized and inhaled by anaesthetized ventilated male guinea pigs (Dunkin-Hartley). Bronchial response to intravenous administration of acetylcholine was determined before and after drug administration and changes in pulmonary resistance at several time-points were expressed as percentage inhibition of bronchospasm.

The compounds of the present invention inhibited the bronchospasm response to acetylcholine with high potency and a long duration of action.

In particular, the preferred quaternary ammonium salts of formula (II) according to the invention have advantageous pharmacokinetic properties.

From the above described results one of ordinary skill in the art can readily understand that the compounds of the present invention have excellent antimuscarinic activity (M3) and thus are useful for the treatment of diseases in which the muscarinic M3 receptor is implicated, including respiratory diseases such as chronic obstructive pulmonary disease, bronchitis, asthma, bronchial hyperreactivity and rhinitis; urinary diseases such as urinary incontinence, pollakiuria, neurogenic bladder, nocturnal enuresis, unstable bladder, cystospasm and chronic cystitis; gastrointestinal diseases such as irritable bowel syndrome, spastic colitis, diverticulitis and peptic ulceration; and cardiovascular disorders such as vagally induced sinus bradicardia.

The present invention further provides a compound of formula (I) or (II) or a pharmaceutically acceptable composition comprising a compound of formula (I) or (II) for use in a method of treatment of the human or animal body by therapy, in particular for the treatment of respiratory, urinary or gastrointestinal disease. The present

invention further provides a compound of formula (I) or (II) or a pharmaceutically acceptable composition comprising a compound of formula (I) or (II) for the manufacture of a medicament for the treatment of respiratory, urinary or gastrointestinal disease.

Further, the compounds of formula (I) or (II) and pharmaceutical compositions comprising a compound of formula (I) or (II) can be used in a method of treating respiratory, urinary or gastrointestinal disease, which method comprises administering to a human or animal patient in need of such treatment an effective amount of a compound of formula (I) or (II) or a pharmaceutical composition comprising a compound of formula (I) or (II).

Further, the compounds of formula (I) or (II) and pharmaceutical compositions comprising a compound of formula (I) or (II) can be used in combination with other drugs effective in the treatment of these diseases. For example with β_2 agonists, steroids, antiallergic drugs, phosphodiesterase IV inhibitors and/or leukotriene D4 (LTD4) inhibitors, for simultaneous, separate or sequential use in the treatment of a respiratory disease.

The present invention therefore provides a combination product comprising

(i) a compound according to the invention; and

(ii) another compound effective in the treatment of a respiratory, urinary or gastrointestinal disease

for simultaneous, separate or sequential use.

The compound (ii) which is effective in the treatment of a respiratory, urinary or gastrointestinal disease may be a β_2 agonist, steroid, antiallergic drug, phosphodiesterase IV inhibitor and/or leukotriene D4 (LTD4) inhibitor. Preferably, the product is for simultaneous, separate or sequential use in the treatment of a respiratory disease.

The present invention will be further illustrated by the following examples. The examples are given by way of illustration only and are not to be construed as limiting.

(3-Fluorobenzyl)-(3-fluorophenyl)carbamic acid (3R)-1-azabicyclo[2.2.2]oct-3-yl ester

The title compound was synthesisesynthesized according to method a. The yield was 3.0 g, 39.1%.

MS [M+1] $^+$: 373

^{1}H-NMR($CDCl_3$): δ 1.20-1.35 (m, 1H), 1.35-1.50 (m, 1H), 1.50-1.60 (m, 1H), 1.60-1.75 (m, 1H), 2.0 (m, 1H), 2.55-2.85 (m, 5H), 3.18-3.27 (m, 1H), 4.79-4.90 (m, 1H), 4.90 (s, 2H), 6.85-7.10 (m, 5H), 7.22-7.35 (m, 3H).

(3R)-3-[(3-Fluorobenzyl)-(3-fluorophenyl)carbamoyloxy]-1-(2-phenoxyethyl)-1-azoniabicyclo[2.2.2]octane bromide

The title compound was synthesisesynthesized according to methods a and c. The yield of the final step was 0.32 g, 69.2%.

m.p.: 142.8-143.6°C

MS [M-Br] $^+$: 493

^{1}H-NMR(DMSO-d_6): δ 1.50-1.70 (m, 1H), 1.70-1.85 (m, 1H), 1.85-2.05 (m, 2H), 2.23 (m, 1H), 3.25-3.40 (m, 1H), 3.40-3.75 (m, 6H), 3.95-4.10 (m, 1H), 4.44 (m, 2H), 4.90-5.10 (m, 3H), 6.90-7.25 (m, 8H), 7.25-7.45 (m, 5H).

(3R)-3-[(3-Fluorobenzyl)-(3-fluorophenyl)carbamoyloxy]-1-(3-phenylpropyl)-1-azoniabicyclo[2.2.2]octane bromide

The title compound was synthesisesynthesized according to methods a and c. The yield of the final step was 0.24 g, 52.1%.

m.p.: 64.5-66.0°C

MS [M-Br] $^+$: 491

^{1}H-NMR(DMSO-d_6): δ 1.50-1.65 (m, 1H), 1.65-1.80 (m, 1H), 1.80-2.10 (m, 4H), 2.20 (m, 1H), 2.60 (t, 2H), 3.05-3.55 (m, 7H), 3.80-3.90 (m, 1H), 4.90-5.10 (m, 3H), 7.05-7.45 (m, 13H).

m-Tolyl-(2,4,5-trifluorobenzyl)carbamic acid (3R)-1-azabicyclo[2.2.2]oct-3-yl ester (described in method (a))

The title compound was synthesized according to method a. The yield was 3.05 g, 29.2%.

MS [M+1]$^+$: 405

^{1}H-NMR ($CDCl_3$): δ 1.22-1.40 (m, 1H), 1.40-1.60 (m, 2H), 1.60-1.75 (m, 1H), 2.0 (m, 1H), 2.32 (s, 3H), 2.60-2.90 (m, 5H), 3.17-3.26 (m, 1H), 4.78-4.83 (m, 1H), 4.86 (s, 2H), 6.82-7.0 (m, 3H), 7.03-7.07 (m, 1H), 7.15-7.25 (m, 2H).

(3R)-1-(2-Phenoxyethyl)-3-[m-tolyl-(2,4,5-trifluorobenzyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane bromide (described in method (c))

The title compound was synthesized according to methods a and c. The yield of the final step was 0.34 g, 75.5%.

m.p.: 137.3-139.1°C

MS [M-Br] $^+$: 525

^{1}H-NMR(DMSO-d_6): δ 1.40-1.70 (m, 1H), 1.70-2.05 (m, 3H), 2.20 (m, 1H), 2.25 (s, 3H), 3.25-3.40 (m, 1H), 3.40-3.80 (m, 6H), 3.95-4.10 (m, 1H), 4.44 (m, 2H), 4.90 (m, 2H), 5.01 (m, 1H), 6.95-7.30 (m, 7H), 7.30-7.60 (m, 4H).

(3R)-1-(3-Phenylpropyl)-3-[m-tolyl-(2,4,5-trifluorobenzyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane bromide

The title compound was synthesisesynthesized according to methods a and c. The yield of the final step was 0.32 g, 72.5%.

m.p.: 113.1-114.8°C

MS [M-Br] $^+$: 523

^{1}H-NMR(DMSO-d_6): δ 1.40-1.60 (m, 1H), 1.60-1.80 (m, 1H), 1.80-2.10 (m, 4H), 2.18 (m, 1H), 2.26 (s, 3H), 2.60 (t, 2H), 3.05-3.55 (m, 7H), 3.80-3.90 (m, 1H), 4.90 (m, 2H), 4.98 (m, 1H), 7.0-7.15 (m, 2H), 7.15-7.40 (m, 7H), 7.40-7.60 (m, 2H).

(3-Fluorophenyl)-(3,4,5-trifluorobenzyl)carbamic acid (3R)-1-azabicyclo[2.2.2]oct-3-yl ester

The title compound was synthesisesynthesized according to method a. The yield was 0.33 g, 8.8%.

MS [M+1] $^+$: 409

^{1}H-NMR($CDCl_3$): δ1.20-1.80 (m, 4H), 2.02 (m, 1H), 2.60-3.05 (m, 5H), 3.25-3.40 (m, 1H), 4.70-4.82 (m, 2H), 4.85-4.90 (m, 1H), 6.80-7.10 (m, 4H), 7.20-7.40 (m, 2H).

(3R)-3-[(3-Fluorophenyl)-(3,4,5-trifluorobenzyl)carbamoyloxy]-1-(2-phenoxyethyl)-1-azoniabicyclo[2.2.2]octane bromide

The title compound was synthesisesynthesized according to methods a and c. The yield of the final step was 0.16 g, 75%.

m.p.: 173.9-175.5°C

MS [M-Br] $^+$: 529

^{1}H-NMR(DMSO-d_6): δ 1.50-2.05 (m, 4H), 2.24 (m, 1H), 3.25-3.85 (m, 7H), 4.03 (m, 1H), 4.45 (m, 2H), 4.95 (m, 2H), 5.04 (m, 1H), 6.95-7.15 (m, 4H), 7.20-7.45 (m, 7H).

Cyclohexylmethyl-(2-fluorophenyl)carbamic acid (3R)-1-azabicyclo[2.2.2]oct-3-yl ester

The title compound was synthesisesynthesized according to method a. The yield was 3.15 g, 42.3%.

MS [M+1] $^{+}$: 361

^{1}H-NMR($CDCl_3$): δ 0.80-1.05 (m, 2H), 1.05-1.80 (m, 13H), 2.0 (m, 1H), 2.55-3.05 (m, 5H), 3.15-3.30 (m, 1H), 3.40-3.60 (m, 2H), 4.70-4.85 (m, 1H), 7.05-7.35 (m, 4H).

(3R)-3-[Cyclohexylmethyl-(2-fluorophenyl)carbamoyloxy]-1-(2-phenoxyethyl)-1-azoniabicyclo[2.2.2]octane bromide

The title compound was synthesisesynthesized according to methods a and c. The yield of the final step was 0.38 g, 81.4%.

m.p.: 73.1-74.5°C

MS [M-Br] $^{+}$: 481

^{1}H-NMR(DMSO-d_6): δ 0.80-1.0 (m, 2H), 1.0-1.20 (m, 3H), 1.20-1.45 (m, 1H), 1.45-1.80 (m, 6H), 1.80-2.20 (m, 4H), 3.05-3.20 (m, 1H), 3.30-3.85 (m, 8H), 3.90-4.10 (m, 1H), 4.35-4.50 (m, 2H), 4.90-5.10 (m, 1H), 6.95-7.10 (m, 3H), 7.20-7.55 (m, 6H).

(3R)-3-[Cyclohexylmethyl-(2-fluorophenyl)carbamoyloxy]-1-(3-phenylpropyl)-1-azoniabicyclo[2.2.2]octane bromide

The title compound was synthesisesynthesized according to methods a and c. The yield of the final step was 0.34 g, 73 %.

m.p.: 73.3-74.1°C

MS [M-Br] $^{+}$: 479

^{1}H-NMR(DMSO-d_6): δ 0.80-1.45 (m, 6H), 1.50-2.20 (m, 12H), 2.57 (m, 2H), 2.90-3.0 (m, 1H), 3.10-3.65 (m, 8H), 3.75-3.95 (m, 1H), 4.90-5.05 (m, 1H), 7.20-7.55 (m, 9H).

[2-(3,4-Dimethoxyphenyl)ethyl]-(5-methylfuran-2-ylmethyl)carbamic acid (3R)-1-azabicyclo[2.2.2]oct-3-yl ester

The title compound was synthesisesynthesized according to method a. The yield was 3.5 g, 61.2%.

MS [M+1] $^{+}$: 429

^{1}H-NMR($CDCl_3$): δ 1.34-1.50 (m, 1H), 1.50-1.64 (m, 1H), 1.64-1.78 (m, 1H), 1.78-1.94 (m, 1H), 2.05 (m, 1H), 2.27 (two singlets, 3H), 2.64-2.84 (m, 5H), 2.84-2.98 (m, 2H),

3.20-3.30 (m, 1H), 3.35-3.60 (m, 2H), 3.82 (s, 6H), 4.28 (m, 1H), 4.36 (m, 1H), 4.76 (m, 1H), 5.89 (m, 1H), 6.03-6.13 (m, 1H), 6.60-6.82 (m, 3H).

(3R)-1-Allyl-3-[[2-(3,4-dimethoxyphenyl)ethyl]-(5-methylfuran-2-ylmethyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane bromide (described in method (c))

The title compound was synthesized according to methods a and c. The yield of the final step was 0.365 g, 94.8%.

MS $[M-Br]^+$: 469

Benzylphenylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester

The title compound was synthesisesynthesized according to method a. The yield of the final step was 1000 mg, 18%. ^{1}H- NMR ($CDCl_3$): δ 1.3-1.7 (m, 4H), 1.9 (s, 1H), 2.5-2.8 (m, 5H), 3.2 (m, 1H), 4.8 (m, 1H), 4.9 (s, 2H), 7.1-7.4 (m, 10H); MS $[M+1]^+$: 337.

3-(R)(Benzylphenylcarbamoyloxy)-1-methyl-1-azoniabicyclo[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 20 mg, 34%. ^{1}H- NMR (DMSO-d_6): δ 1.54-1.90 (m, 4H), 2.17 (s, 1H), 2.95 (s, 3H), 3.22-3.52 (m, 5H), 3.84 (m, 1H), 4.92 (s, 2H), 4.99 (m, 1H), 7.12-7.37 (m, 10H); MS $[M-CF_3COO]^+$: 351.

3-(R)(Benzylphenylcarbamoyloxy)-1-(4-methylpent-3-enyl)-1-azoniabicyclo[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 18 mg, 25%. MS $[M-CF_3COO]^+$: 419.

3-(R)(Benzylphenylcarbamoyloxy)-1-(3-phenoxypropyl)-1-azoniabicyclo-[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 21 mg, 26%. ^{1}H- NMR (DMSO-d_6) : δ 1.56-1.91 (m, 4H), 2.11-2.20 (m, 3H), 3.12 (m, 1H), 3.34-3.51 (m, 6H), 3.86 (m, 1H), 4.06 (m, 2H), 4.93 (s, 2H), 5.02 (m, 1H), 6.97 (m, 3H), 7.20-7.38 (m, 12H); MS $[M-CF_3COO]^+$: 471.

3-(R)(Benzylphenylcarbamoyloxy)-1-(3-phenylallyl)-1-azoniabicyclo[2.2.2]octane bromide

The title compound was synthesisesynthesized according to method c. The yield of the final step was 220 mg, 70%. ^{1}H- NMR (DMSO-d_6) : δ 1.55-1.92 (m, 4H), 2.21 (s, 1H), 3.15 (m, 1H), 3.34-3.50 (m, 5H), 3.90 (m, 1H), 4.1 (m, 2 H), 4.02 (s, 2 H), 5.05 (m, 1H), 6.49 (m, 1H), 6.85-6.90 (d, 1H), 7.20-7.59 (m, 12H), 7.59-7.61 (m, 2H); MS [M-Br]$^+$: 453; mp : 129°C.

1-Allyl-3-(R)(benzylphenylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane bromide

The title compound was synthesisesynthesized according to method c. The yield of the final step was 230 mg, 85%. ^{1}H- NMR (DMSO-d_6): δ 1.58-1.91 (m, 4H), 2.20 (s, 1H), 3.10 (m, 1H), 3.27-3.41 (m, 4H), 3.79-3.90 (m, 3H), 4.92 (s, 2H), 5.03 (m, 1H), 5.61 (m, 2H), 5.98 (m, 1H), 7.20-7.38 (m, 10H); MS [M-Br]$^+$: 377; mp : 70°C.

3-(R)(Benzylphenylcarbamoyloxy)-1-(2-hydroxyethyl)-1-azoniabicyclo [2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 12 mg, 19%. MS [M-CF_3COO]$^+$: 381.

3-(R)(Benzylphenylcarbamoyloxy)-1-isopropyl-1-azoniabicyclo[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 17 mg, 26%. ^{1}H- NMR (DMSO-d_6): δ 1.24 (m, 6H), 1.64-1.89 (m, 4H), 2.20 (s, 1H), 2.78 (m, 1H), 3.23-3.32 (m, 4H), 3.50 (m, 1H), 3.76 (m, 1H), 4.92 (s, 2H), 5.06 (m, 1H), 7.20-7.38 (m, 10H); MS [M-CF_3COO]$^+$: 379.

3-(R)(Benzylphenylcarbamoyloxy)-1-propyl-1-azoniabicyclo[2.2.2]octane-trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 16 mg, 25%. ^{1}H- NMR (DMSO-d_6) : δ0.88 (m, 3H), 1.57-1.68 (m, 4H), 1.89 (m, 2H), 2.18 (s, 1H), 2.99-3.14 (m, 3H), 3.26-3.40 (m, 4H), 3.83 (m, 1H), 4.92 (s, 2H), 5.01 (m, 1H), 7.20-7.37 (m, 10H); MS [M-CF_3COO]$^+$: 379.

3-(R)(Benzylphenylcarbamoyloxy)-1-(3-cyanopropyl)-1-azoniabicyclo[2.2.2]-octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 13 mg, 19%. ^{1}H- NMR (DMSO-d_6) : δ 1.67-2.07 (m, 6H), 2.19 (s, 1H),

2.60 (m, 2H), 3.07 (m, 1H), 3.21-3.48 (m, 6H), 3.85 (m, 1H), 4.92 (s, 2H), 5.01 (m, 1H), 7.20-7.37 (m, 10); MS $[M\text{-}CF_3COO]^+$: 404.

3-(R)(Benzylphenylcarbamoyloxy)-1-cyclopropylmethyl-1-azoniabicyclo[2.2.2]-octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 9 mg, 14%. MS $[M\text{-}CF_3COO]^+$: 391.

3-(R)(Benzylphenylcarbamoyloxy)-1-(2-ethoxyethyl)-1-azoniabicyclo[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 22 mg, 32%. ^{1}H- NMR (DMSO-d_6) : δ 1.12 (m, 3H), 1.58-1.90 (m, 4H), 2.19 (s, 1H), 3.12-3.15 (m, 1H), 3.28-3.53 (m, 8H), 3.75 (m, 2H), 3.90 (m, 1H), 4.91 (s, 2H), 5.02 (m, 1H), 7.20-7.37 (m, 10H); MS $[M\text{-}CF_3COO]^+$: 409.

3-(R)(Benzylphenylcarbamoyloxy)-1-(4-ethoxycarbonylbutyl)-1-azoniabicyclo-[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 14 mg, 18%. ^{1}H- NMR (DMSO-d_6) : δ 1.19 (m, 3H), 1.50-1.67 (m, 4H), 1.85-1.88 (m, 2H), 2.18 (s, 1H), 2.38 (m, 2H), 3.99 (m, 1H), 3.16-3.42 (m, 8H), 3.82 (m, 1H), 4.06 (m, 2H), 4.92 (s, 2H), 5.02 (m, 1H), 7.19-7.37 (m, 10H); MS $[M\text{-}CF_3COO]^+$: 465.

3-(R)(Benzylphenylcarbamoyloxy)-1-(4-phenylbutyl)-1-azoniabicyclo[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 14 mg, 18%. ^{1}H- NMR (DMSO-d_6) : δ 1.57-1.65 (m, 6H), 1.88 (m, 2H), 2.18 (s, 1H), 2.63 (m, 2H), 3.00 (m, 1H), 3.18-3.42 (m, 6H), 3.79-3.86 (m, 1H), 4.94 (s, 2H), 5.00 (m, 1H), 7.18-7.37 (m, 15H); MS $[M\text{-}CF_3COO]^+$: 469.

3-(R)(Benzylphenylcarbamoyloxy)-1-[3-(4-fluorophenoxy)propyl]-1-azoniabicyclo-[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 21 mg, 25%. ^{1}H- NMR (DMSO-d_6) : δ 1.55-1.91 (m, 4H), 2.10-2.20 (m, 3H), 3.10 (m, 1H), 3.28-3.50 (m, 6H), 3.88 (m, 1H), 4.02 (m, 2H), 4.93 (s, 2H), 5.02 (m, 1H), 6.95-7.12 (m, 2H), 7.12-7.38 (m, 12H); MS $[M\text{-}CF_3COO]^+$: 489.

3-(R)(Benzylphenylcarbamoyloxy)-1-(3-hydroxypropyl)-1-azoniabicyclo[2.2.2]-octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 12 mg, 18%. ^{1}H- NMR (DMSO-d_6) : δ 1.54-1.88 (m, 6H), 2.18 (s, 1H), 3.09 (m, 1H), 3.23-3.49 (m, 8H), 3.85 (m, 1H), 4.84 (m, OH), 4.92 (s, 2H), 5.02 (m, 1H), 7.19-7.37 (m, 10H); MS [M-CF_3COO]$^+$: 395.

1-(4-Acetoxybutyl)-3-(R)(benzylphenylcarbamoyloxy)-1-azoniabicyclo[2.2.2]-octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 9 mg, 12%. ^{1}H- NMR (DMSO-d_6) : δ 1.40-1.70 (m, 5H), 1.81-1.91 (m, 3H), 2.02 (m, 3H), 2.19 (s, 1H), 3.03 (m, 1H), 3.19 (m, 2H), 3.26-3.46 (m, 4H), 3.80-3.84 (m, 1H), 4.04 (m, 2H), 4.92 (s, 2H), 5.01-5.02 (m, 1H), 7.19-7.37 (m, 10H); MS [M-CF_3COO]$^+$: 451.

3-(R)(Benzylphenylcarbamoyloxy)-1-(4-oxo-4-thiophen-2-ylbutyl)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 16 mg, 19%. ^{1}H- NMR (DMSO-d_6) : δ 1.55-1.69 (m, 2H), 1.87-2.05 (m, 4H), 2.19 (s, 1H), 3.09 (m, 3H), 3.22 (m, 2H), 3.29-3.46 (m, 4H), 3.88 (m, 1H), 4.93 (s, 2H), 5.02 (m, 1H), 7.19-7.38 (m, 11H), 7.98-8.06 (m, 2H); MS [M-CF_3COO]$^+$: 489.

3-(R)(Benzylphenylcarbamoyloxy)-1-[3-(3-hydroxyphenoxy)propyl]-1-azonia-bicyclo[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 17 mg, 21%. ^{1}H- NMR (DMSO-d_6) : δ 1.57-1.68 (m, 2H), 1.90 (m, 2H), 2.08-2.19 (m, 3H), 3.11 (m, 1H), 3.28-3.50 (m, 6H), 3.88 (m, 1H), 3.97 (m, 2H), 4.93 (s, 2H), 5.02 (m, 1H), 6.33-6.40 (m, 3H), 7.04 (m, 1H), 7.20-7.38 (m, 10H), 9.5 (s, OH); MS [M-CF_3COO]$^+$: 487.

3-(R)(Benzylphenylcarbamoyloxy)-1-heptyl-1-azoniabicyclo[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 17 mg, 23%. ^{1}H- NMR (DMSO-d_6) : δ 0.88 (m, 3H), 1.28 (m, 8H), 1.62 (m, 4H), 1.85-1.88 (m, 2H), 2.18 (s, 1H), 3.02 (m, 1H), 3.15 (m, 2H), 3.26-3.40 (m, 4H), 3.83 (m, 1H), 4.92 (s, 2H), 5.01 (m, 1H), 7.20-7.37 (m, 10H); MS [M-CF_3COO]$^+$: 435.

1-(2-Benzyloxyethyl)-3-(R)(benzylphenylcarbamoyloxy)-1-azoniabicyclo[2.2.2]-octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 20 mg, 25%. ^{1}H- NMR (DMSO-d_6) : δ 1.54-1.94 (m, 4H), 2.20 (s, 1H), 3.17 (m, 1H), 3.28-3.55 (m, 6H), 3.85 (m, 2H), 9.92-3.99 (m, 1H), 4.53 (s, 2H), 4.91 (s, 2H), 5.02 (m, 1H), 7.18-7.40 (m, 15H); MS [M-CF_3COO]$^+$: 471.

Benzyl-(4-fluorophenyl)carbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester

The title compound was synthesisesynthesized according to method a. The yield of the final step was 1110 mg, 13%. ^{1}H- NMR (DMSO-d_6) : δ 1.16-1.52 (m, 4H), 1.81 (s, 1H), 2.42-2.57 (m, 5H), 2.99-3.07 (m, 1H), 4.63 (m, 1H), 4.84 (s, 2H), 7.10-7.32 (m, 9H); MS [M+1] : 355.

1-Allyl-3-(R)[benzyl-(4-fluorophenyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 10 mg, 23%. MS [M-CF_3COO]$^+$: 395.

3-(R)[Benzyl-(4-fluorophenyl)carbamoyloxy]-1-(3-phenylpropyl)-1-azoniabicyclo [2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 13 mg, 25%. MS [M-CF_3COO]$^+$: 473.

Benzyl-p-tolylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester

The title compound was synthesisesynthesized according to method a. The yield of the final step was 1070 mg, 11%. ^{1}H- NMR (DMSO-d_6) : δ 1.18-1.30 (m, 2H), 1.45-1.55 (m, 2H), 1.83 (s, 1H), 2.25 (s, 3H), 2.43-2.59 (m, 5H), 3.01-3.10 (m, 1H), 4.64 (m, 1H), 4.85 (s, 2H), 7.12-7.34 (m, 9H); MS [M+1]$^+$: 351.

1-Allyl-3-(R)(benzyl-p-tolylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 9 mg, 19%. MS [M-CF_3COO]$^+$: 391.

3-(R)(Benzyl-p-tolylcarbamoyloxy)-1-(3-phenylpropyl)-1-azoniabicyclo[2.2.2]-octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 13 mg, 25%. MS [M- CF_3COO]$^+$: 469.

3-(R)(Benzylphenylcarbamoyloxy)-1-[2-(2-methoxyethoxy)ethyl]-1-azoniabicyclo[2.2.2]octane bromide

The title compound was synthesisesynthesized according to method c. The yield of the final step was 390 mg, 84%. ^{1}H- NMR (DMSO-d_6) : δ 1.55-1.75 (m, 2 H), 1.88 (m, 2H), 2.17 (s, 1H), 3.14 (m, 1H), 3.22 (s, 3H), 3.29-3.55 (m, 10H), 3.78 (m, 2H), 3.90 (m, 1H), 4.89 (s, 2H), 4.99 (m, 1H), 7.17-7.35 (m, 10H); MS [M-Br]$^+$: 439.

3-(R)(Benzylphenylcarbamoyloxy)-1-phenethyl-1-azoniabicyclo[2.2.2]octane bromide

The title compound was synthesisesynthesized according to method c. The yield of the final step was 200 mg, 65%. ^{1}H- NMR (DMSO-d_6) : δ 1.55-1.75 (m, 2H), 1.90 (m, 2H), 2.19 (s, 1H), 3.00 (m, 2H), 3.10 (m, 1H), 3.31-3.51 (m, 6H), 3.90 (m, 1H), 4.91 (s, 2H), 5.04 (m, 1H), 7.18-7.37 (m, 15H). MS [M-Br]$^+$: 441; mp 81°C.

3-(R)(Benzylphenylcarbamoyloxy)-1-(3-thiophen-2-ylpropyl)-1-azoniabicyclo-[2.2.2]octane bromide

The title compound was synthesisesynthesized according to method c. The yield of the final step was 970 mg, 82%. ^{1}H- NMR (DMSO-d_6) : δ 1.55-1.69 (m, 2H), 1.85-2.04 (m, 4H), 2.18 (s, 1H), 2.83 (m, 2H), 3.01 (m, 1H), 3.20-3.44 (m, 6H), 3.85 (m, 1H), 4.92 (s, 2H), 5.00 (m, 1H), 6.94-7.00 (m, 2 H), 7.19-7.40 (m, 11H). MS [M-Br]$^+$: 461; mp 95°C.

3-(R)(Benzylphenylcarbamoyloxy)-1-(3-phenylpropyl)-1-azoniabicyclo[2.2.2]-octane bromide

The title compound was synthesisesynthesized according to method c. The yield of the final step was 880 mg, 79%. ^{1}H- NMR (DMSO-d_6) : δ 1.55-1.69 (m, 2H), 1.85-2.00 (m, 4H), 2.18 (s, 1H), 2.59 (m, 2H), 3.04 (m, 1H), 3.23-3.44 (m, 6H), 3.85 (m, 1H), 4.92 (s, 2H), 5.02 (m, 1H), 7.18-7.36 (m, 15H).); MS [M-Br]$^+$: 455; mp 101°C.

3-(R)(Benzylphenylcarbamoyloxy)-1-(2-phenoxyethyl)-1-azoniabicyclo[2.2.2]-octane bromide

The title compound was synthesisesynthesized according to method c. The yield of the final step was 360 mg, 67%. ^{1}H- NMR (DMSO-d_6) : δ 1.5-1.73 (m, 2H), 1.89 (m, 2H),

2.20 (s, 1H), 3.23 (m, 1H), 3.46-3.72 (m, 6H), 4.02 (m, 1H), 4.43 (m, 2H), 4.92 (s, 2H), 5.03 (m, 1H), 7.01 (m, 3H), 7.17-7.38 (m, 12H); MS $[M\text{-}Br]^+$: 457; mp 117°C.

3-(R)(Benzylphenylcarbamoyloxy)-1-[3-(3-cyanophenoxy)propyl]-1-azoniabicyclo-[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 16 mg, 36%; MS $[M\text{- } CF_3COO\ ]^+$: 496.

3-(R)(Benzylphenylcarbamoyloxy)-1-[3-(naphthalen-1-yloxy)propyl]-1-azonia-bicyclo[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 10 mg, 21%; MS $[M\text{- } CF_3COO\ ]^+$: 521.

3-(R)(Benzylphenylcarbamoyloxy)-1-[3-(methylphenylamino)propyl]-1-azonia-bicyclo[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 12 mg, 28%; MS $[M\text{- } CF_3COO\ ]^+$: 484.

3-(R)(Benzylphenylcarbamoyloxy)-1-(3-phenylsulfsulphanylpropyl)-1-azoniabicyclo[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 8 mg, 18%; ^{1}H- NMR (DMSO-d_6) : δ 1.45-2.00 (m, 6H), 2.17 (bs, 1H), 3.00 (m, 2H), 3.28-3.41 (m, 7H), 3.83 (m, 1H), 4.91 (s, 2H), 4.98 (m, 1H), 7.18-7.41 (m, 15H); MS $[M\text{- } CF_3COO]^+$: 487.

3-(R)(Benzylphenylcarbamoyloxy)-1-(4-oxo-4-phenylbutyl)-1-azoniabicyclo[2.2.2]-octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 10 mg, 23%; ^{1}H- NMR (DMSO-d_6) : δ 1.50-2.06 (m, 6H), 2.20 (bs, 1H), 3.13-3.47 (m, 9H), 3.89 (m, 1H), 4.93 (s, 2H), 5.02 (m, 1H), 7.19-7.38 (m, 10H), 7.54-7.70 (m, 3H), 7.98-8.00 (m, 2H); MS $[M\text{- } CF_3COO]^+$: 483.

3-(R)(Benzylphenylcarbamoyloxy)-1-[3-(2,4,6-trimethylphenoxy)propyl]-1-azonia-bicyclo[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 14 mg, 30%; ^{1}H- NMR (DMSO-d_6) : δ 1.50-2.20 (m, 7H), 2.19 (s, 9H),

3.16-3.52 (m, 7H), 3.73 (m, 2H), 3.92 (m, 1H), 4.93 (s, 2H), 5.03 (m, 1H), 6.83 (s, 2H), 7.19-7.38 (m, 10H); MS [M- CF_3COO]$^+$: 513.

3-(R)(Benzylphenylcarbamoyloxy)-1-[3-(2-chlorophenoxy)propyl]-1-azonia-bicyclo[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 14 mg, 31%; MS [M- CF_3COO]$^+$: 506.

3-(R)(Benzylphenylcarbamoyloxy)-1-[3-(3-trifluoromethylphenoxy)propyl]-1-azoniabicyclo[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 14 mg, 29%; ^{1}H- NMR (DMSO-d_6) : δ 1.50-2.00 (m, 4H), 2.08-2.20 (m, 3H), 3.12-3.50 (m, 7H), 3.90 (m, 1H), 4.14 (m, 2H), 4.93 (s, 2H), 5.03 (m, 1H), 7.19-7.38 (m, 13H), 7.54-7.59 (m, 1H). MS [M- CF_3COO]$^+$: 539.

3-(R)(Benzylphenylcarbamoyloxy)-1-[3-(biphenyl-4-yloxy)propyl]-1-azoniabicyclo-[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 12 mg, 24%; ^{1}H- NMR (DMSO-d_6) : δ 1.50-2.20 (m, 7H), 3.14 (bs, 1H), 3.28-3.52 (m, 6 H), 3.91 (m, 1H), 4.10 (m, 2H), 4.93 (s, 2H), 5.03 (m, 1H), 7.03-7.08 (m, 2H), 7.18-7.47 (m, 13H), 7.61-7.65 (m, 4H); MS [M- CF_3COO]$^+$: 547.

3-(R)(Benzylphenylcarbamoyloxy)-1-[3-(2,4-difluorophenoxy)propyl]-1-azonia-bicyclo[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 10 mg, 22%; ^{1}H- NMR (DMSO-d_6) : δ 1.50-2.19 (m, 7H), 3.10 (bs, 1H), 3.28-3.51 (m, 6H), 3.90 (m, 1H), 4.10 (m, 2H), 4.93 (s, 2H), 5.02 (m, 1H), 7.02-7.09 (m, 1H), 7.19-7.37 (m, 12H); MS [M- CF_3COO]$^+$: 507.

3-(R)(Benzylphenylcarbamoyloxy)-1-[3-(4-methoxyphenoxy)propyl]-1-azonia-bicyclo[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 10 mg, 22%; ^{1}H- NMR (DMSO-d_6) : 1.50-2.19 (m, 7H), 3.11 (bs, 1H), 3.28-3.51 (m, 6H), 3.70 (s, 3H), 3.89 (m, 1H), 3.94-3.99 (m, 2H), 4.93 (s, 2H), 5.02 (m, 1H), 6.85-6.92 (m, 4H), 7.19-7.38 (m, 10H); MS [M- CF_3COO]$^+$: 501.

3-(R)(Benzylphenylcarbamoyloxy)-1-[3-(5,6,7,8-tetrahydronaphthalen-2-yloxy)-propyl]-1-azoniabicyclo[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 10 mg, 21%; ^{1}H- NMR (DMSO-d_6) : δ 1.50-1.71 (m, 6H), 1.87-2.19 (m, 5H), 2.63-2.68 (m, 4H), 3.10 (bs, 1H), 3.28-3.50 (m, 6H), 3.88 (m, 1H), 3.98 (m, 2H), 4.93 (s, 2H), 5.02 (m, 1H), 6.63-6.70 (m, 2H), 6.95-6.98 (d, 1H), 7.19-7.38 (m, 10H); MS [M-CF_3COO]$^+$: 525.

1-[3-(Benzo[1,3]dioxol-5-yloxy)propyl]-3-(R)(benzylphenylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 12 mg, 26%; MS [M- CF_3COO]$^+$: 515.

3-(R)(Benzylphenylcarbamoyloxy)-1-[3-(2-carbamoylphenoxy)propyl]-1-azonia-bicyclo[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 10 mg, 22%; ^{1}H- NMR (DMSO-d_6) : δ 1.50-2.27 (m, 7H), 3.09 (bs, 1H), 3.28-3.48 (m, 6H), 3.88 (m, 1H), 4.14 (m, 2H), 4.93 (s, 2H), 5.04 (m, 1H),7.02-7.15 (m, 2H), 7.19-7.38 (m, 10H), 7.44-7.50 (m, 1H), 7.55(bs, NH_2), 7.69-7.72 (dd,1H); MS [M-CF_3COO]$^+$: 514.

3-(R)(Benzylphenylcarbamoyloxy)-1-[3-(3-dimethylaminophenoxy)propyl]-1-azoniabicyclo[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 12 mg, 26%; MS [M- CF_3COO]$^+$: 514.

1-[3-(4-Acetylaminophenoxy)propyl]-3-(R)(benzylphenylcarbamoyloxy)-1-azonia bicyclo[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 12 mg, 25%; ^{1}H- NMR (DMSO-d_6) : δ 1.50-1.92 (m, 4H), 2.01 (s, 3H), 2.04-2.20 (m, 3H), 3.12 (bs, 1H), 3.28-3.51 (m, 6H), 3.89 (m, 1H), 4.00 (m, 2H), 4.93 (s, 2H), 5.02 (m, 1H), 6.86-6.91 (m, 2H), 7.19-7.38 (m, 10H), 7.48-7.53 (m. 2H), 9.85 (s,NH); MS [M-CF_3COO]$^+$: 528.

3-(R)(Benzylphenylcarbamoyloxy)-1-[3-(4-methoxycarbonylphenoxy)propyl]-1-azoniabicyclo[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 12 mg, 25%; ^{1}H- NMR (DMSO-d_6) : δ 1.50-2.20 (m, 7H), 3.12 (bs, 1H), 3.29-3.51 (m, 6H), 3.82 (s, 3H), 3.87-3.93 (m, 1H), 4.14 (m, 2H), 4.93 (s, 2H), 5.03(m, 1H), 7.04-7.09 (m, 2H), 7.19-7.38 (m, 10H), 7.92-7.96 (m, 2H); MS [M- CF_3COO]$^+$: 529.

3-(R)(Benzylphenylcarbamoyloxy)-1-[3-(4-nitrophenoxy)propyl]-1-azoniabicyclo-[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 12 mg, 26%; ^{1}H- NMR (DMSO-d_6) : δ 1.50-2.27 (m, 7H), 3.12 (bs, 1H), 3.29-3.51 (m, 6H), 3.87-3.94 (m, 1H), 4.21 (m, 2H), 4.93 (s, 2H), 5.03 (m, 1H), 7.14-7.38 (m, 12H), 8.22-8.28 (m, 2H); MS [M- CF_3COO]$^+$: 516.

3-(R)(Benzylphenylcarbamoyloxy)-1-[3-(4-hydroxymethylphenoxy)propyl]-1-azoniabicyclo[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 10 mg, 22%; MS [M- CF_3COO]$^+$: 501.

Benzylphenylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(S)yl ester

The title compound was synthesisesynthesized according to method a. The yield of the final step was 1000 mg, 23%; ^{1}H- NMR (DMSO-d_6) : δ 1.14-1.57 (m, 4H), 1.83 (bs, 1H), 2.43-2.61 (m, 5H), 2.61 -3.01 (m, 1H), 4.64 (m, 1H), 4.89 (s, 2H), 7.16-7.35 (m, 10H). MS [M+1]$^+$: 337.

3-(S)(Benzylphenylcarbamoyloxy)-1-(3-phenylpropyl)-1-azoniabicyclo[2.2.2]-octane bromide

The title compound was synthesisesynthesized according to method c. The yield of the final step was 660 mg, 83%.^{1}H- NMR (DMSO-d_6) : δ 1.40-2.00 (m, 6H), 2.18 (bs, 1H), 2.59 (m, 2H), 2.95-3.44 (m, 7H), 3.84 (m, 1H), 4.92 (s, 2H), 5.00 (m, 1H), 7.19-7.36 (m, 15H). MS [M- Br]$^+$: 455; mp : 64°C.

Butylphenylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester

The title compound was synthesized according to method a. The yield of the final step was 1880 mg, 22%; ^{1}H- NMR ($CDCl_3$) : δ 0.9 (m, 3H), 1.3 (m, 4H), 1.5 (m, 4H), 1.9 (s, 1H), 2.7 (m, 5H), 3.2 (m, 1H), 3.7 (m, 2H), 4.7 (m, 1H), 7.2-7.4 (m, 5H); MS [M+1]$^+$: 303.

3-(R)(Butylphenylcarbamoyloxy)-1-methyl-1-azoniabicyclo[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 16 mg, 30%; MS [M- CF_3COO]$^+$: 317.

3-(R)(Butylphenylcarbamoyloxy)-1-(4-methylpent-3-enyl)-1-azoniabicyclo[2.2.2]-octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 18 mg, 27%; MS [M- CF_3COO]$^+$: 385.

3-(R)(Butylphenylcarbamoyloxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]-octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 21 mg, 28%; MS [M- CF_3COO]$^+$: 437.

3-(R)(Butylphenylcarbamoyloxy)-1-(3-phenylallyl)-1-azoniabicyclo[2.2.2]octane bromide

The title compound was synthesisesynthesized according to method c. The yield of the final step was 182 mg, 48%; ^{1}H- NMR (DMSO-d_6) : δ 0.84 (m, 3H), 1.25 (m, 2H), 1.40 (m, 2H), 1.70-1.91 (m, 4H), 2.20 (s, 1H), 3.2-3.4 (m, 6 H), 3.64 (m, 2H), 3.88 (m, 1H), 3.88-4.07 (d, 2H), 4.97 (m, 1H), 6.45 (m, 1H), 6.83-6.88 (d, 1H), 7.23-7.45 (m, 7H), 7.60 (m, 2H); MS [M- Br]$^+$: 419; mp : 144°C

1-Allyl-3-(R)(butylphenylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane bromide

The title compound was synthesisesynthesized according to method c. The yield of the final step was 200 mg, 72%; ^{1}H- NMR (DMSO-d_6) : δ 0.85 (m, 3H), 1.21-1.34 (m, 3H), 1.40-1.45 (m, 2H), 1.70-2.18 (m, 4H), 3.15-3.40 (m, 5H), 3.61-3.67 (m, 2H), 3.82 (m, 1H), 3.92-3.94 (m, 2H), 4.95 (m, 1H), 5.62 (m, 2H), 5.97-6.01 (m, 1H), 7.26-7.44 (m, 5H); MS [M- Br]$^+$: 343; mp : 141°C.

3(R)(Butylphenylcarbamoyloxy)-1-(2-hydroxyethyl)-1-azoniabicyclo[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was13 mg, 19%; MS [M- CF_3COO]$^+$: 347.

3-(R)(Butylphenylcarbamoyloxy)-1-isopropyl-1-azoniabicyclo[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 20 mg, 29%; MS [M- CF_3COO]$^+$: 345.

3-(R)(Butylphenylcarbamoyloxy)-1-propyl-1-azoniabicyclo[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 16 mg, 23%; MS [M- CF_3COO]$^+$: 345.

3-(R)(Butylphenylcarbamoyloxy)-1-(3-cyanopropyl)-1-azoniabicyclo[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 15 mg, 20%; MS [M- CF_3COO]$^+$: 370.

3-(R)(Butylphenylcarbamoyloxy)-1-cyclopropylmethyl-1-azoniabicyclo[2.2.2]-octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 2 mg, 3%; MS [M- CF_3COO]$^+$: 357.

3-(R)(Butylphenylcarbamoyloxy)-1-(2-ethoxyethyl)-1-azoniabicyclo[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 19 mg, 25%; MS [M- CF_3COO]$^+$: 375.

3-(R)(Butylphenylcarbamoyloxy)-1-(4-ethoxycarbonylbutyl)-1-azoniabicyclo[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 12 mg, 14%; MS [M- CF_3COO]$^+$: 431.

3-(R)(Butylphenylcarbamoyloxy)-1-(3-hydroxypropyl)-1-azoniabicyclo[2.2.2]-octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 12 mg, 17%; MS [M- CF_3COO]$^+$: 361.

3-(R)(Butylphenylcarbamoyloxy)-1-(3-pyrrol-1-ylpropyl)-1-azoniabicyclo[2.2.2]-octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 19 mg, 23%; MS [M- CF_3COO]$^+$: 410.

1-(4-Acetoxybutyl)-3-(R)(butylphenylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 10 mg, 12%; MS [M- CF_3COO]$^+$: 417.

3-(R)(Butylphenylcarbamoyloxy)-1-(4-oxo-4-thiophen-2-ylbutyl)-1-azoniabicyclo-[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 17 mg, 19%; MS [M- CF_3COO]$^+$: 455.

3-(R)(Butylphenylcarbamoyloxy)-1-(4-phenylbutyl)-1-azoniabicyclo[2.2.2]octane-trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 17 mg, 20%; MS [M- CF_3COO]$^+$: 435.

3-(R)(Butylphenylcarbamoyloxy)-1-[3-(3-hydroxyphenoxy)propyl]-1-azoniabicyclo[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 21 mg, 23%; MS [M- CF_3COO]$^+$: 453.

3-(R)(Butylphenylcarbamoyloxy)-1-heptyl-1-azoniabicyclo[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 17 mg, 21%; MS [M- CF_3COO]$^+$: 401.

1-(2-Benzyloxyethyl)-3-(R)(butylphenylcarbamoyloxy)-1-azoniabicyclo[2.2.2]-octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 22 mg, 25%; MS [M- CF_3COO]$^+$: 437.

3-(R)(Butylphenylcarbamoyloxy)-1-phenethyl-1-azoniabicyclo[2.2.2]octane bromide

The title compound was synthesisesynthesized according to method c. The yield of the final step was 330 mg, 82%; ^{1}H- NMR (DMSO-d_6) : δ 0.83 (m, 3H), 1.27-1.34 (m, 2H), 1.41-1.48 (m, 3H), 1.60-2.23 (m, 4H), 2.96-3.47 (m, 7H), 3.57-3.71 (m, 4H), 3.92 (m, 1H), 4.98 (m, 1H), 7.25-7.45 (m, 10H); MS [M- Br]$^+$: 407; mp : 139°C

3-(R)(Butylphenylcarbamoyloxy)-1-[2-(2-methoxyethoxy)ethyl]-1-azoniabicyclo-[2.2.2]octane bromide

The title compound was synthesisesynthesized according to method c. The yield of the final step was 520 mg, 81%; ^{1}H- NMR (DMSO-d_6) : δ 0.82 (m, 3H), 1.24-1.31 (m, 2H), 1.39-1.47 (m, 2H), 1.70-2.20 (m, 5 H), 3.26 (s, 3H), 3.35-3.70 (m, 13H), 3.82-3.86 (m, 3H), 4.94 (m, 1H), 7.26-7.44 (m, 5 H); MS [M- Br]$^+$: 405.

Butyl-(4-fluorophenyl)carbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester

The title compound was synthesisesynthesized according to method a. The yield of the final step was 1650 mg, 24%; ^{1}H- NMR (DMSO-d_6) : δ 0.82 (m, 3H), 1.20-1.54 (m, 8H), 1.83 (m, 1H), 2.49-2.70) (m, 5H), 3.02-3.09 (m, 1H), 3.36-3.63 (m, 2H), 4.59 (m, 1H), 7.19-7.35 (m, 4H). ; MS [M+1]$^+$: 321.

3-(R)(Butylphenylcarbamoyloxy)-1-[3-(4-fluorophenoxy)propyl]-1-azoniabicyclo-[2.2.2]octane chloride

The title compound was synthesisesynthesized according to method c. The yield of the final step was 390 mg, 75%; ^{1}H- NMR (DMSO-d_6) : δ 0.82 (m, 3H), 1.26-1.31 (m, 2H), 1.40-1.48 (m, 2H), 1.70-2.17 (m, 5H), 3.20-3.7 (m, 11H), 3.86 (m, 1H), 4.02 (m, 2H), 4.94 (m, 1H), 6.95-7.00 (m, 2H), 7.12-7.18 (m, 2H), 7.26-7.44 (m, 5H); MS [M- Cl]$^+$: 455; mp: 126°C.

3-(R)(Butylphenylcarbamoyloxy)-1-(2-phenoxyethyl)-1-azoniabicyclo[2.2.2]octane bromide

The title compound was synthesisesynthesized according to method c. The yield of the final step was 260 mg, 53%; ^{1}H- NMR (DMSO-d_6) : δ 0.84 (m, 3H), 1.23-1.30 (m, 2H), 1.39-1.48 (m, 2H), 1.70-2.20 (m, 5H), 3.20-3.72 (m, 9H), 3.99 (m, 1H), 4.44 (m, 2H), 4.95 (m, 1H), 7.01 (m, 3H), 7.24-7.40 (m, 7H); MS [M- Br]$^+$: 423; mp : 153°C.

3-(R)(Butylphenylcarbamoyloxy)-1-(3-thiophen-2-ylpropyl)-1-azoniabicyclo-[2.2.2]octane bromide

The title compound was synthesisesynthesized according to method c. The yield of the final step was 1100 mg, 62%; ^{1}H- NMR (DMSO-d_6) : δ 0.84 (m, 3H), 1.24-1.31 (m, 2H), 1.42 (m, 2H), 1.60-2.21 (m, 7H), 2.85 (m, 2H), 3.0-3.50 (m, 7H), 3.60-3.69 (m, 2H), 3.85 (m, 1H), 4.93 (m, 1H), 6.95-7.00 (m, 2H), 7.28-7.43 (m, 6H); MS [M- Br]$^+$: 427; mp: 127°C.

3-(R)(Butylphenylcarbamoyloxy)-1-(3-phenylpropyl)-1-azoniabicyclo[2.2.2]octane bromide

The title compound was synthesisesynthesized according to method c. The yield of the final step was 280 mg, 56%; ^{1}H- NMR (DMSO-d_6) : δ 0.84 (m, 3H), 1.23-1.33 (m, 2H), 1.43 (m, 2H), 1.60-2.20 (m, 7H), 2.59 (m, 2H), 3.00-3.78 (m, 9H), 3.84 (m, 1H), 4.92 (m, 1H), 7.20-7.42 (m, 10H); MS [M- Br]$^+$: 421; mp : 120°C.

Phenylthiophen-2-ylmethylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester

The title compound was synthesisesynthesized according to method a. The yield of the final step was 310 mg, 10%; ^{1}H- NMR (DMSO-d_6) : δ 1.10-1.60 (m, 4 H), 1.87 (s, 1H), 2.46-2.63 (m, 5H), 3.04-3.33 (m, 1H), 4.66 (m, 1H), 5.01 (s, 2H), 6.87-6.94 (m, 2H), 7.20-7.43 (m, 6H); MS [M+1]$^+$: 343.

1-Methyl-3-(R)(phenylthiophen-2-ylmethylcarbamoyloxy)-1-azoniabicyclo[2.2.2]-octane bromide

The title compound was synthesisesynthesized according to method c. The yield of the final step was 160 mg, 80%; ^{1}H- NMR (DMSO-d_6) : 1.65-2.00 (m, 4H), 2.20 (s, 1 H), 2.98 (s, 3H), 3.32-3.52 (m, 5H), 3.85-3.92 (m, 1H), 4.98-5.04 (m, 3H), 6.94 (m, 2H), 7.24-7.45 (m, 6H).; MS [M- Br]$^+$: 357.

1-(3-Phenoxypropyl)-3-(R)(phenylthiophen-2-ylmethylcarbamoyloxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 16 mg, 42%; MS [M- CF_3COO]$^+$: 477.

1-(3-Phenylpropyl)-3-(R)(phenylthiophen-2-ylmethylcarbamoyloxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 13 mg, 35%; ^{1}H- NMR (DMSO-d_6) : δ 1.72-2.3 (m, 7H), 2.58 (m, 2H), 3.00-3.48 (m, 7H), 3.84 (m, 1H), 5.04 (m, 3H), 6.92-6.94 (m, 2H), 7.20-7.43 (m, 11H); MS [M- CF_3COO]$^+$: 461.

1-(3-Phenylallyl)-3-(R)(phenylthiophen-2-ylmethylcarbamoyloxy)-1-azoniabicyclo-[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 4 mg, 11%; MS [M- CF_3COO]$^+$: 459.

1-(2-Benzyloxyethyl)-3-(R)(phenylthiophen-2-ylmethylcarbamoyloxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 14 mg, 37%; MS [M- CF_3COO]$^+$: 477.

1-[3-(3-Hydroxyphenoxy)propyl]-3-(R)(phenylthiophen-2-ylmethylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 11 mg, 28%; MS [M- CF_3COO]$^+$: 493.

1-Heptyl-3-(R)(phenylthiophen-2-ylmethylcarbamoyloxy)-1-azoniabicyclo[2.2.2]-octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 13 mg, 37%; MS [M- CF_3COO]$^+$: 441.

3-(R)(Phenylthiophen-2-ylmethylcarbamoyloxy)-1-(3-thiophen-2-ylpropyl)-1-azoniabicyclo[2.2.2]octane bromide

The title compound was synthesisesynthesized according to method c. The yield of the final step was 140 mg, 48%; ^{1}H- NMR (DMSO-d_6) : δ 1.40-2.30 (m, 7H), 2.83 (m, 2H), 3.00-3.60 (m, 7H), 3.88 (m, 1H), 5.04 (m, 3H), 6.93-6.99 (m, 4H), 7.28-7.43 (m, 7H); MS [M- Br]$^+$: 467.

1-(2-Phenoxyethyl)-3-(R)(phenylthiophen-2-ylmethylcarbamoyloxy)-1-azonia-bicyclo[2.2.2]octane bromide

The title compound was synthesisesynthesized according to method c. The yield of the final step was 510 mg, 80%; ^{1}H- NMR (DMSO-d_6) : δ 1.40-2.30 (m, 5H), 3.20-3.73 (m, 7H), 4.05 (m, 1H), 4.44 (bs, 2H), 5.04 (m, 3H), 6.91-7.04 (m, 5H), 7.24-7.41 (m, 8H); MS [M- Br]$^+$: 463; mp : 133°C.

1-Allyl-3-(R)(phenylthiophen-2-ylmethylcarbamoyloxy)-1-azoniabicyclo[2.2.2]-octane bromide

The title compound was synthesisesynthesized according to method c. The yield of the final step was 360 mg, 66%; ^{1}H- NMR (DMSO-d_6) : δ 1.40-2.30 (m, 5H), 3.00-3.41 (m, 5H), 3.81-3.92 (m, 3H), 5.04 (m, 3H), 5.61 (m, 2H), 5.93-6.05 (m, 1H), 6.93-6.96 (m, 2H), 7.24-7.46 (m, 6H); MS [M- Br]$^+$: 383; mp : 110°C.

Phenethylphenylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester

The title compound was synthesisesynthesized according to method a. The yield of the final step was 1400 mg, 17%; ^{1}H- NMR (DMSO-d_6) : δ 1.10-1.60 (m, 4H), 1.83 (s, 1H), 2.40-2.70 (m, 5H), 2.78 (m, 2H), 3.00-3.08 (m, 1H), 3.87 (m, 2H), 4.58 (m, 1H), 7.16-7.40 (m, 10H); MS [M+1]$^+$: 351.

1-Methyl-3-(R)(phenethylphenylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane bromide

The title compound was synthesisesynthesized according to method c. The yield of the final step was 140 mg, 73%; ^{1}H- NMR (DMSO-d_6) : δ 1.40-2.30 (m, 5H), 2.80 (m, 2H), 2.94 (s, 3H), 3.10-3.50 (m, 5H), 3.78-3.95 (m, 3H), 4.89 (m, 1H), 7.16-7.41 (m, 10H); MS [M- Br]$^+$: 365; mp : 203°C.

1-Allyl-3-(R)(phenethylphenylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 11 mg, 35%; MS [M- CF_3COO]$^+$: 391.

3-(R)(Phenethylphenylcarbamoyloxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]-octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 16 mg, 41%; MS [M- CF_3COO]$^+$: 485.

3-(R)(Phenethylphenylcarbamoyloxy)-1-(2-phenoxyethyl)-1-azoniabicyclo[2.2.2]-octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 15 mg, 40%; ^{1}H- NMR (DMSO-d_6) : δ 1.45-2.18 (m, 5H), 2.81 (m, 2H), 3.28-3.70 (m, 7H), 3.80-4.02 (m, 3H), 4.43 (m, 2H), 4.95 (m, 1H), 6.98-7.04 (m, 2H), 7.16-7.40 m, 13H); MS [M- CF_3COO]$^+$: 471.

3-(R)(Phenethylphenylcarbamoyloxy)-1-(3-phenylpropyl)-1-azoniabicyclo[2.2.2]-octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 14 mg, 37%; ^{1}H- NMR (DMSO-d_6) : δ 1.45-2.20 (m, 7H), 2.59 (m, 2H), 2.81 (m, 2H), 3.05-3.5 (m, 7H), 3.78-3.89 (m, 3H), 4.91 (m, 1H), 7.17-7.42 (m, 15H); MS [M- CF_3COO]$^+$: 469.

3-(R)(Phenethylphenylcarbamoyloxy)-1-(3-phenylallyl)-1-azoniabicyclo[2.2.2]-octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 4 mg, 11%; MS [M- CF_3COO]$^+$: 467.

1-(2-Benzyloxyethyl)-3-(R)(phenethylphenylcarbamoyloxy)-1-azoniabicyclo-[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 14 mg, 36%; MS [M- CF_3COO]$^+$: 485.

1-[3-(3-Hydroxyphenoxy)propyl]-3-(R)(phenethylphenylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 14 mg, 35%; ^{1}H- NMR (DMSO-d_6) : δ 1.45-2.20 (m, 7H), 2.82 (m, 2H), 3.05-3.50 (m, 7H), 3.83-3.99 (m, 5H), 4.94 (m, 1H), 6.33-6.39 (m, 3H), 7.04-7.09 (m, 1H), 7.18-7.44(m, 10H), 9.49 (s, OH); MS [M- CF_3COO]$^+$: 501.

1-Heptyl-3-(R)(phenethylphenylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 15 mg, 42%; ^{1}H- NMR (DMSO-d_6) : δ 0.88 (m, 3H), 1.28 (m, 8H), 1.55-2.20 (m, 7H), 2.82 (m, 2H), 3.00-3.50 (m, 7H), 3.68-3.89 (m, 3H), 4.92 (m, 1H), 7.18-7.43 (m, 10H); MS [M- CF_3COO]$^+$: 449.

3-(R)(Phenethylphenylcarbamoyloxy)-1-(3-thiophen-2-ylpropyl)-1-azoniabicyclo-[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 15 mg, 39%; MS [M- CF_3COO]$^+$: 475.

Pentylphenylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester

The title compound was synthesisesynthesized according to method a. The yield of the final step was 620 mg, 9%; ^{1}H- NMR (DMSO-d_6) : δ 0.83 (m, 3H), 1.22-1.30 (m, 5H), 1.43-1.56 (m, 5H), 1.83 (s, 1H), 2.42-2.65 (m, 5H), 3.01-3.06 (m, 1H), 3.59-3.65 (m, 2H), 4.49 (m, 1H), 7.22-7.41 (m, 5 H); MS [M+1]$^+$: 317.

1-Methyl-3-(R)(pentylphenylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane bromide

The title compound was synthesisesynthesized according to method c. The yield of the final step was 130 mg, 68%; ^{1}H- NMR (DMSO-d_6) : δ 0.81 (m, 3H), 1.21 (m, 5H), 1.45-2.20 (m, 6H), 2.93 (s, 3H), 3.10-3.70 (m, 7H), 3.80 (m, 1 H), 4.88 (m, 1H), 7.24-7.41 (m, 5H); MS [M-Br]$^+$: 331.

1-Allyl-3-(R)(pentylphenylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to the method. The yield of the final step was 10 mg, 35%; ^{1}H- NMR (DMSO-d_6): δ 0.83 (m, 3H), 1.21-1.28 (m, 4H), 1.46 (m, 3H), 1.54-1.91 (m, 3H), 2.30 (m, 1H), 3.28-3.41 (m, 5H), 3.78-3.92 (m, 5H), 4.94 (m, 1H), 5.54-5.64 (m, 2H), 5.98 (m, 1H), 7.26-7.43 (m, 5H); MS [M- CF_3COO]$^+$: 357.

3-(R)(Pentylphenylcarbamoyloxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]-octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 13 mg, 36%; MS [M- CF_3COO]$^+$: 451.

3-(R)(Pentylphenylcarbamoyloxy)-1-(2-phenoxyethyl)-1-azoniabicyclo[2.2.2]-octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 14 mg, 40%; ^{1}H- NMR (DMSO-d_6): δ 0.82 (m, 3H), 1.23 (m, 4H), 1.46 (m, 3H), 1.54-1.91 (m, 3H), 2.25 (s, 1H), 3.28-3.70 (m, 9H), 3.98 (m, 1H), 4.43 (m, 2H), 4.95 (m, 1H), 6.98-7.04 (m, 3H), 7.23-7.4 (m, 7H); MS [M- CF_3COO]$^+$: 437.

3-(R)(Pentylphenylcarbamoyloxy)-1-(3-phenylpropyl)-1-azoniabicyclo[2.2.2]-octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 13 mg, 37%; ^{1}H- NMR (DMSO-d_6): δ 0.82 (m, 3H), 1.20-1.25 (m, 5H), 1.44 (m, 3H), 1.68-2.13 (m, 7H), 2.58 (m, 2H), 3.00-3.41 (m, 5H), 3.54-3.69 (m, 2H), 3.79-3.85 (m, 1H), 4.92 (m, 1H), 7.20-7.42 (m, 10H); MS [M- CF_3COO]$^+$: 435.

3-(R)(Pentylphenylcarbamoyloxy)-1-(3-phenylallyl)-1-azoniabicyclo[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 4 mg, 12%; MS [M- CF_3COO]$^+$: 433.

1-(2-Benzyloxyethyl)-3-(R)(pentylphenylcarbamoyloxy)-1-azoniabicyclo[2.2.2]-octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 15 mg, 42%; MS [M- CF_3COO]$^+$: 451.

1-[3-(3-Hydroxyphenoxy)propyl]-3-(R)(pentylphenylcarbamoyloxy)-1-azonia-bicyclo [2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 12 mg, 32%; MS [M- CF_3COO]$^+$: 467.

1-Heptyl-3-(R)(pentylphenylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 15 mg, 45%; MS [M- CF_3COO]$^+$: 415.

3-(R)(Pentylphenylcarbamoyloxy)-1-(3-thiophen-2-ylpropyl)-1-azoniabicyclo-[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 13 mg, 37%; ^{1}H- NMR (DMSO-d_6): δ 0.82 (m, 3H), 1.22-1.26 (m, 5H), 1.46 (m, 3H), 1.60-2.14 (m, 7H), 2.82 (m, 2H),3.20-3.41 (m, 5H), 3.50-3.70 (m, 2H), 3.82 (m, 1H), 4.92 (m, 1H), 6.93-6.99 (m, 2 H), 7.25-7.43 (m, 6H); MS [M- CF_3COO]$^+$: 441.

Pent-4-enylphenylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester

The title compound was synthesisesynthesized according to method a. The yield of the final step was 690 mg, 14%; ^{1}H- NMR (DMSO-d_6): δ 1.10-1.60 (m, 6 H), 1.84 (bs, 1H), 1.97-2.04 (m, 2H), 2.45-2.65 (m, 5H), 3.02-3.10 (m, 1H), 3.29-3.66 (m, 2H), 4.59 (m, 1H), 4.61-5.00 (m, 2H), 5.70-5.84 (m, 1H), 7.22-7.42 (m, 5H); MS [M+1]$^+$: 315.

1-Allyl-3-(R)(pent-4-enylphenylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 10 mg, 35%; MS [M- CF_3COO]$^+$: 355.

3-(R)(Pent-4-enylphenylcarbamoyloxy)-1-(3-phenoxypropyl)-1-azoniabicyclo-[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 15 mg, 42%; ^{1}H- NMR (DMSO-d_6): δ 1.50-2.20 (m, 11H), 3.23-3.47 (m, 7H), 3.56-3.73 (m, 2H), 3.87 (m, 1H), 4.03 (m, 2H), 4.92-4.95 (m, 2H), 5.00 (m, 1H), 5.70-5.82 (m, 1H), 6.93-6.99 (m, 2H), 7.26-7.44 (m, 8H); MS [M- CF_3COO]$^+$: 449.

3-(R)(Pent-4-enylphenylcarbamoyloxy)-1-(2-phenoxyethyl)-1-azoniabicyclo-[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 13 mg, 37%; ^{1}H- NMR (DMSO-d_6): δ 1.55 (m, 2H), 1.65-2.20 (m, 7H), 3.28-3.75 (m, 9H), 3.98 (m, 1H), 4.43 (bs, 2H), 4.92-4.99 (m, 3H), 5.70-5.83 (m, 1H), 6.98-7.04 (m, 3H), 7.24-7.40 (m, 7H); MS [M- CF_3COO]$^+$: 435.

3-(R)(Pent-4-enylphenylcarbamoyloxy)-1-(3-phenylpropyl)-1-azoniabicyclo[2.2.2]-octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 13 mg, 37%; ^{1}H- NMR (DMSO-d_6): δ 1.56 (m, 3H), 1.70-2.14 (m, 8H), 2.58 (m, 2H), 3.19-3.41 (m, 7H), 3.56-3.71 (m, 2H), 3.81 (m, 1H), 4.92-4.99 (m, 3H), 5.70-5.83 (m, 1H), 7.20-7.43 (m, 10H); MS [M- CF_3COO]$^+$: 433.

3-(R)(Pent-4-enylphenylcarbamoyloxy)-1-(3-phenylallyl)-1-azoniabicyclo[2.2.2]-octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 4 mg, 12%; MS [M- CF_3COO]$^+$: 431.

1-(2-Benzyloxyethyl)-3-(R)(pent-4-enylphenylcarbamoyloxy)-1-azoniabicyclo-[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 16 mg, 44%; MS [M- CF_3COO]$^+$: 449.

1-[3-(3-Hydroxyphenoxy)propyl]-3-(R)(pent-4-enylphenylcarbamoyloxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 12 mg, 32%; MS [M- CF_3COO]$^+$: 465.

1-Heptyl-3-(R)(pent-4-enylphenylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane-trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 3 mg, 9%; MS [M- CF_3COO]$^+$: 413.

1-Methyl-3-(R)(pent-4-enylphenylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 13 mg, 49%; MS [M- CF_3COO]$^+$: 429.

3-(R)(Pent-4-enylphenylcarbamoyloxy)-1-(3-thiophen-2-ylpropyl)-1-azoniabicyclo-[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 15 mg, 43%; ^{1}H- NMR (DMSO-d_6): δ 1.40-2.20 (m, 11H), 2.82 (m, 2H), 3.05-3.5 (m, 7H), 3.58-3.86 (m, 3H), 4.92-4.95 (m, 2H) 5.00 (m, 1H), 5.70-5.84 (m, 1H), 6.93-7.00 (m, 2H), 7.26-7.44 (m, 6H); MS [M- CF_3COO]$^+$: 439.

Phenylthiophen-3-ylmethylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester

The title compound was synthesisesynthesized according to method a. The yield of the final step was 2000 mg, 15%; ^{1}H- NMR (DMSO-d_6): δ 1.10-1.60 (m, 4H), 1.84 (bs, 1H), 2.46-2.62 (m, 5H), 3.02-3.10 (m, 1H), 4.62-4.67 (m, 1H), 4.84 (s, 2H), 6.99 (m, 1H), 7.18-7.36 (m, 6H), 7.47-7.50 (m, 1H).; MS [M+1]$^+$: 343.

1-Allyl-3-(R)(phenylthiophen-3-ylmethylcarbamoyloxy)-1-azoniabicyclo[2.2.2]-octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 8 mg, 26%; ^{1}H- NMR (DMSO-d_6): δ 1.45-2.00 (m, 4H), 2.21 (bs, 1H), 3.04-3.42 (m, 5H), 3.78-3.91 (m, 3H), 4.87 (s, 2H), 5.02 (m, 1H), 5.54-5.64 (m, 2H), 5.91-6.02 (m, 1H), 7.00-7.02 (m, 1H), 7.22-7.39 (m, 6H), 7.50-7.52 (m, 1H); MS [M- CF_3COO]$^+$: 383.

1-(3-Phenoxypropyl)-3-(R)(phenylthiophen-3-ylmethylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 12 mg, 31%; MS [M- CF_3COO]$^+$: 477.

1-(3-Phenylpropyl)-3-(R)(phenylthiophen-3-ylmethylcarbamoyloxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 15 mg, 41%; ^{1}H- NMR (DMSO-d_6): δ 1.45-2.18 (m, 7H), 2.59 (m, 2H), 3.02-3.44 (m, 7H), 3.84 (m, 1H), 4.87 (s, 2H), 4.99 (m, 1H), 7.00 (m, 1H), 7.21-7.38 (m, 11H), 7.47-7.50 (m, 1H); MS [M- CF_3COO]$^+$: 461.

1-(3-Phenylallyl)-3-(R)(phenylthiophen-3-ylmethylcarbamoyloxy)-1-azoniabicyclo-[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 4 mg, 11%; MS [M- CF_3COO]$^+$: 459.

1-(2-Benzyloxyethyl)-3-(R)(phenylthiophen-3-ylmethylcarbamoyloxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 16 mg, 42%; MS [M- CF_3COO]$^+$: 477.

1-[3-(3-Hydroxyphenoxy)propyl]-3-(R)(phenylthiophen-3-ylmethylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 13 mg, 33%; MS [M- CF_3COO]$^+$: 493.

1-Heptyl-3-(R)(phenylthiophen-3-ylmethylcarbamoyloxy)-1-azoniabicyclo[2.2.2]-octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 12 mg, 34%; ^{1}H-NMR (DMSO-d_6): δ 0.88 (m, 3H), 1.28 (m, 8H), 1.60-2.19 (m, 7H), 3.00-3.41 (m, 7H), 3.83 (m, 1H), 4.88 (s, 2H), 5.99 (m, 1H), 7.01 (m, 1H), 7.21-7.39 (m, 6H), 7.49-7.52 (m, 1H); MS [M- CF_3COO]$^+$: 441.

1-Methyl-3-(R)(phenylthiophen-3-ylmethylcarbamoyloxy)-1-azoniabicyclo[2.2.2]-octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 12 mg, 42%; MS [M- CF_3COO]$^+$: 357.

3-(R)(Phenylthiophen-3-ylmethylcarbamoyloxy)-1-(3-thiophen-2-ylpropyl)-1-azoniabicyclo[2.2.2]octane bromide

The title compound was synthesisesynthesized according to method c. The yield of the final step was 500 mg, 78%; ^{1}H- NMR (DMSO-d_6): δ 1.45-2.19 (m, 7H), 2.83 (m, 2H), 3.04-3.13 (m, 1H), 3.19-3.46 (m, 6H), 3.83-3.90 (m, 1H), 4.88 (s, 2H), 4.99 (m, 1H), 6.94 (m, 3H), 7.20-7.40 (m, 7H), 7.49 (m, 1H); MS [M- Br]$^+$: 467; mp : 110°C.

3-(R)(Phenylthiophen-3-ylmethylcarbamoyloxy)-1-(2-phenoxyethyl)-1-azonia-bicyclo[2.2.2]octane bromide

The title compound was synthesisesynthesized according to method c. The yield of the final step was 350 mg, 63%; ^{1}H- NMR (DMSO-d_6): δ 1.45-2.20 (m, 5H), 3.27 (m, 1H), 3.40-3.80 (m, 6H), 4.00-4.06 (m, 1H), 4.44 (bs, 2H), 4.87 (s, 2H), 5.02 (m, 1H), 6.99-7.04 (m, 4H), 7.20-7.38 (m, 8H), 7.48 (m, 1H); MS [M- Br]$^+$: 463; mp : 131°C.

Butylthiophen-2-ylmethylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester

The title compound was synthesisesynthesized according to method a. The yield of the final step was 1300 mg, 29%; ^{1}H- NMR (DMSO-d_6): δ 0.85 (m, 3H), 1.19-1.68 (m, 8H), 1.92 (m, 1H), 2.49-2.64 (m, 5H), 3.05-3.22 (m, 3H), 4.56-4.62 (m, 3H), 6.95-7.04 (m, 2H), 7.42-7.44 (m, 1H); MS [M+1]$^+$: 323.

1-Allyl-3-(R)(butylthiophen-2-ylmethylcarbamoyloxy)-1-azoniabicyclo[2.2.2]-octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 10 mg, 23%; ^{1}H- NMR (DMSO-d_6): δ 0.86 (m, 3H), 1.20-1.26 (m, 2H), 1.42-1.49 (m, 2H), 1.58-2.05 (m, 4H), 2.32 (bs, 1H), 3.20-3.41 (m, 7H), 3.74-3.94 (m, 3H), 4.51-4.72 (m, 2H), 4.99 (m, 1H), 5.55-5.64 (m, 2H), 5.87-6.10 (m, 1H), 6.99 (m, 1H), 7.08 (m, 1H), 7.46 (m, 1H); MS [M- CF_3COO]$^+$: 363.

3-(R)(Butylthiophen-2-ylmethylcarbamoyloxy)-1-(3-phenylpropyl)-1-azoniabicyclo[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 13 mg, 25%; ^{1}H- NMR (DMSO-d_6): δ 0.85 (m, 3H), 1.19-1.26 (m, 2H),1.41-1.50 (m, 2H), 1.75-2.10 (m, 6H), 2.30 (bs, 1H), 2.59 (m, 2H), 3.10-3.50 (m, 9H), 3.83 (m, 1 H), 4.50-4.74 (m, 2H), 4.97 (m, 1H), 6.97 (m, 1H), 7.07 (m, 1H), 7.20-7.35 (m, 5H), 7.43 (m, 1H); MS [M- CF_3COO]$^+$: 441.

bis-Thiophen-2-ylmethylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester

The title compound was synthesisesynthesized according to method a. The yield of the final step was 340 mg, 7%; ^{1}H- NMR (DMSO-d_6): δ 1.28-1.31 (m, 1H), 1.45-1.72 (m, 3H), 1.94-1.97 (m, 1H), 2.49-2.71 (m, 5H), 3.06-3.14 (m, 1H), 4.50-4.57 (m, 4H), 4.62-4.69 (m, 1H), 6.96-7.06 (m, 4H), 7.44-7.46 (m, 2H); MS $[M+1]^+$: 363.

1-Allyl-3-(R)(bis-thiophen-2-ylmethylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 9 mg, 19%; ^{1}H- NMR (DMSO-d_6): δ 1.70-2.06 (m, 4H), 2.35 (bs, 1H), 3.25-3.50 (m, 5H), 3.80-3.94 (m, 3H), 4.54-4.71 (m, 4H), 5.10 (m, 1H), 5.55-5.65 (m, 2H), 5.87-6.10 (m, 1H), 6.98-7.01 (m, 2H), 7.06-7.10 (m, 2H), 7.47-7.48 (m, 2H); MS [M- CF_3COO]$^+$: 403.

3-(R)(bis-thiophen-2-ylmethylcarbamoyloxy)-1-(3-phenylpropyl)-1-azoniabicyclo-[2.2.2]octane bromide

The title compound was synthesisesynthesized according to method c. The yield of the final step was 690 mg, 82%; ^{1}H- NMR (DMSO-d_6): δ 1.78-2.10 (m, 6H), 2.34 (bs, 1H), 2.53-2.63 (m, 2H), 3.23-3.48 (m, 7H), 3.88 (m, 1H), 4.53-4.74 (m, 4H), 5.05 (m, 1H), 6.98-7.01 (m, 2H), 7.02-7.11 (m, 2H), 7.21-7.37 (m, 5H), 7.44-7.48 (m, 2H); MS [M-Br]$^+$: 481.

Furan-2-ylmethyl-2-thiophen-2-ylmethylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester

The title compound was synthesisesynthesized according to method a. The yield of the final step was 700 mg, 10%; ^{1}H- NMR (DMSO-d_6): δ 1.10-1.34 (m, 1H), 1.44-1.67 (m, 3H), 1.93 (bs, 1H), 2.50-2.70 (m, 5H), 3.05-3.12 (m, 1H), 3.37-4.40 (m, 2H), 4.57-4.66 (m, 3H), 6.26-6.42 (m, 2H), 6.95-7.03 (m, 2H), 7.45 (m, 1H), 7.61 (m, 1H); MS $[M+1]^+$: 347.

1-Allyl-3-(R)(furan-2-ylmethylthiophen-2-ylmethylcarbamoyloxy)-1-azoniabicyclo-[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 7 mg, 15%; MS [M- CF_3COO]$^+$: 387.

3-(R)(Furan-2-ylmethylthiophen-2-ylmethylcarbamoyloxy)-1-(3-phenylpropyl)-1-azoniabicyclo[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 11 mg, 20%; ^{1}H- NMR (DMSO-d_6): δ 1.70-2.10 (m, 6H), 2.31 (bs, 1H), 2.59 (m, 2H), 3.15-3.50 (m, 7H), 3.84 (m, 1H), 4.36-4.56 (m, 4H), 5.03 (m, 1H), 6.32-6.44 (m, 2H), 6.92-7.08 (m, 2H), 7.20-7.35 (m, 5H), 7.41-7.46 (m, 1H), 7.59-7.62 m, 1H); MS [M- CF_3COO]$^+$: 465.

3-(R)(bis-Thiophen-2-ylmethylcarbamoyloxy)-1-(3-thiophen-2-ylpropyl)-1-azoniabicyclo[2.2.2]octane bromide

The title compound was synthesized according to method c. The yield of the final step was 690 mg, 81%; ^{1}H-NMR (DMSO-d_6): δ 1.78-2.10 (m, 6H), 2.34 (bs, 1H), 2.82 (m, 2H), 3.21-3.46 (m, 7H), 3.89 (m, 1H), 4.54 (m, 4H), 5.06 (m, 1H), 6.95-7.01 (m, 4H), 7.07-7.11 (m, 2H), 7.38-7.49 (m, 3H); MS [M-Br]$^+$: 487; m.p. : 143°C.

Allylthiophen-2-ylmethylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester

The title compound was synthesisesynthesized according to method a. The yield of the final step was 3220 mg, 30%; ^{1}H- NMR (DMSO-d_6): δ 1.20-1.33 (m, 1H), 1.45-1.80 (m, 3H), 1.93 (bs, 1H), 2.49-2.72 (m, 5H), 3.05-3.09 (m, 1H), 3.81-3.83 (m, 2H), 3.83-4.55 (m, 3H), 5.14 (m, 2H), 5.70-5.82 (m, 1H), 6.96-7.04 (m, 2H), 7.44-7.45 (m, 1H); MS [M+1]$^+$: 307.

1-Allyl-3-(R)(allylthiophen-2-ylmethylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 10 mg, 24%; ^{1}H- NMR (DMSO-d_6): δ 1.80-2.10 (m, 4H), 2.32 (bs, 1H), 3.20-3.50 (m, 5H), 3.75-3.94 (m, 5H), 4.5-4.69 (m, 2H), 5.01 (m, 1H), 5.10-5.23 (m, 2H), 5.51-5.65 (m, 2H), 5.70-5.85 (m, 1H), 5.90-6.08 (m, 1H), 6.95-7.10 (m, 2H), 7.47 (m, 1H); MS [M- CF_3COO]$^+$: 347.

3-(R)(Allylthiophen-2-ylmethylcarbamoyloxy)-1-(3-phenylpropyl)-1-azoniabicyclo-[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 11 mg, 22%; ^{1}H- NMR (DMSO-d_6): δ 1.74-2.10 m, 6H), 2.31 (bs, 1H), 2.59 (m, 2H), 3.16-3.56 (m, 7H), 3.76-3.90 (m, 3H), 4.48-4.71 (m, 2H), 4.99 (m, 1H),

5.11-5.23 (m, 2H), 5.72-5.83 (m, 1H), 6.98 (m, 1H), 7.06-7.07(m, 1H), 7.20-7.35 (m, 5H), 7.44 (m, 1H); MS [M- CF_3COO]$^+$: 425.

Cyclopentylthiophen-2-ylmethylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester

The title compound was synthesized according to method a. The yield of the final step was 2250 mg, 33%; ^{1}H- NMR (DMSO-d_6): δ 1.20-1.40 (m, 1H), 1.45-1.72 (m, 11H), 1.89 (bs, 1H), 2.45-2.62 (m, 5H), 3.03-3.10 (m, 1H), 4.22 (bs, 1H), 4.50-4.56 (m, 3H), 6.93-6.99 (m, 2H), 7.38 (m, 1H); MS [M+1]$^+$: 355.

1-Allyl-3-(R)(cyclopentylthiophen-2-ylmethylcarbamoyloxy)-1-azoniabicyclo-[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 10 mg, 22%; ^{1}H- NMR (DMSO-d_6): δ 1.40-2.05 (m, 12H), 2.27 (bs, 1H), 3.03-3.42 (m, 5H),3.70-3.95 (m, 3H), 4.15-4.35 (m, 1H), 5.58 (m, 2H), 4.99 (m, 1H),5.54-5.65 (m, 2H), 5.87-6.10 (m, 1H), 6.97 (m, 1H), 7.03 (m, 1H), 7.41-7.43 (m, 1H); MS [M- CF_3COO]$^+$: 375.

3-(R)(Cyclopentylthiophen-2-ylmethylcarbamoyloxy)-1-(3-phenylpropyl)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 13 mg, 24%; ^{1}H- NMR (DMSO-d_6): δ 1.40-2.10 (m, 14H), 2.25 (bs, 1H), 2.58 (m, 2H), 2.95-3.50 (m, 7H), 3.81 (m, 1H), 4.26 (m, 1H), 4.50-4.70 (m, 2H), 4.97 (m, 1H), 6.93 (m, 1H), 7.03 (m, 1H), 7.20-7.40 (m, 6H); MS [M- CF_3COO]$^+$: 453.

Furan-2-ylmethylphenylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester

The title compound was synthesisesynthesized according to method a. The yield of the final step was 1400 mg, 18%; ^{1}H- NMR (DMSO-d_6): δ 1.19-1.60 (m, 4H), 1.84 (bs, 1H), 2.44-2.57 (m, 5H), 3.01-3.09 (m, 1H), 4.63 (m, 1H), 4.82 (s, 2H), 6.21 (m, 1H), 6.36 (m, 1H), 7.20-7.37 (m, 5H), 7.59 (m, 1H); MS [M+1]$^+$: 327.

1-Allyl-3-(R)(furan-2-ylmethylphenylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 7 mg, 16%; ^{1}H- NMR (DMSO-d_6): δ ; MS [M- CF_3COO]$^+$: 367.

3-(R)(Furan-2-ylmethylphenylcarbamoyloxy)-1-(3-phenylpropyl)-1-azoniabicyclo-[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 11 mg, 21%; ^{1}H- NMR (DMSO-d_6): δ 1.65-2.10 (m, 6H), 2.19 (bs, 1H), 2.59 (m, 2H), 3.10-3.50 (m, 7H), 3.83 (m, 1H), 4.85 (bs, 2H), 4.98 (m, 1H), 6.26 (m, 1H), 6.36 (m, 1H), 7.20-7.39 (m, 10H), 7.59 (m, 1H); MS [M- CF_3COO]$^+$: 445.

bis-Furan-2-ylmethylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester

The title compound was synthesisesynthesized according to method a. The yield of the final step was 2100 mg, 22%; ^{1}H- NMR (DMSO-d_6): δ 1.20-1.70 (m, 4H), 1.89 (bs, 1H), 2.45-2.71 (m, 5H), 3.00-3.12 (m, 1H), 4.40 (m, 4H), 4.62 (m, 1H), 6.22-6.40 (m, 4H), 7.59 (m, 2H); MS [M+1]$^+$: 331.

1-Allyl-3-(R)(bis-furan-2-ylmethylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 7 mg, 16%; ^{1}H- NMR (DMSO-d_6): δ ; MS [M- CF_3COO]$^+$: 371.

3-(R)(bis-furan-2-ylmethylcarbamoyloxy)-1-(3-phenylpropyl)-1-azoniabicyclo-[2.2.2]octane trifluoroacetate

The title compound was synthesisesynthesized according to method d. The yield of the final step was 11 mg, 20%; ^{1}H- NMR (DMSO-d_6): δ 1.70-2.10 (m, 6H), 2.29 (bs, 1H), 2.59 (m, 2H), 3.10-3.50 (m, 7H), 3.82 (m, 1H), 4.32-4.54 (m, 4H), 5.01 (m, 1H), 6.29-6.41 (m, 4H), 7.20-7.35 (m, 5H), 7.57-7.61 (m, 2H); MS [M- CF_3COO]$^+$: 449.

Benzylphenylcarbamic acid 1-azabicyclo[2.2.1]hept-4-yl ester

The title compound was synthesized according to method a. The yield of the final step was 4.86 mg, 1.3%, as formate; ^{1}H- NMR (DMSO-d_6): δ 1.86 (m, 4H), 2.65 (s, 2H), 2.77 (bs, 2H), 3.03 (bs, 2H), 4.84 (s, 2H), 7.14-7.32 (m, 10H), 8.19 (s, 1H): MS [M-HCOO]$^+$: 323.

Benzylphenylcarbamic acid 1-azabicyclo[2.2.2]oct-4-yl ester

The title compound was synthesisesynthesized according to method a. The yield of the final step was 2.56 mg, 1%, as formate; ^{1}H- NMR (DMSO-d_6): δ 1.81 (m, 6H), 2.83 (m, 6H), 4.81 (s, 2H), 7.14-7.32 (m, 10H), 8.24, (s, 1H); MS [M-HCOO]$^+$: 337

The following examples illustrate pharmaceutical compositions according to the present invention and procedures for their preparation.

Preparation of a pharmaceutical composition: tablets

Formulation:

Compound of the present invention.....5.0 mg
Lactose .....113.6 mg
Microcrystalline cellulose.....28.4 mg
Colloidal silica dioxide .....1.5 mg
Magnesium stearate.....1.5 mg

Using a mixer machine, 15 g of the compound of the present invention was mixed with 340.8 g of lactose and 85.2 g of microcrystalline cellulose. The mixture was subjected to compression moulding using a roller compactor to give a flake-like compressed material. The flake-like compressed material was pulverized using a hammer mill, and the pulverized material was screened through a 20 mesh screen. A 4.5 g portion of colloidal silica dioxide and 4.5 g of magnesium stearate were added to the screened material and mixed. The mixer product was subjected to a tablet-making machine equipped with a die/punch system of 7.5 mm in diameter, thereby obtaining 3,000 tablets each having 150 mg in weight.

Preparation of a pharmaceutical composition: coated tablets

Formulation:

Compound of the present invention.....5.0 mg
Lactose .....95.2 mg
Corn starch .....40.8 mg
Polyvinylpyrrolidone .....7.5 mg
Magnesium stearate.....1.5 mg
Hydroxypropylcellulose .....2.3 mg
Polyethylene glycol .....0.4 mg
Titanium dioxide.....1.1 mg
Purified talc .....0.7 mg

Using a fluidized bed granulating machine, 15 g of the compound of the present invention was mixed with 285.6 g of lactose and 122.4 g of corn starch. Separately, 22.5 g of polyvinylpyrrolidone was dissolved in 127.5 g of water to prepare a binding solution. Using a fluidized bed granulating machine, the binding solution was sprayed

on the above mixture to give granulates. A 4.5 g portion of magnesium stearate was added to the obtained granulates and mixed. The obtained mixture was subjected to a tablet-making machine equipped with a die/punch biconcave system of 6.5 mm in diameter, thereby obtaining 3,000 tablets, each having 150 mg in weight.

Separately, a coating solution was prepared by suspending 6.9 g of hydroxypropylmethylcellulose 2910, 1.2 g of polyethylene glycol 6000, 3.3 g of titanium dioxide and 2.1 g of purified talc in 72.6 g of water. Using a High Coated, the 3,000 tablets prepared above were coated with the coating solution to give film-coated tablets, each having 154.5 mg in weight.

Preparation of a pharmaceutical composition: liquid inhalant

Formulation:

Compound of the present invention..... 400 μg

Physiological saline..... 1 ml

A 40 mg portion of the compound of the present invention was dissolved in 90 ml of physiological saline, and the solution was adjusted to a total volume of 100 ml with the same saline solution, dispensed in 1 ml portions into 1 ml capacity ampoules and then sterilized at 115° for 30 minutes to give liquid inhalant.

Preparation of a pharmaceutical composition: powder inhalant

Formulation:

Compound of the present invention..... 200 μg

Lactose ..... 4,000 μg

A 20 g portion of the compound of the present invention was uniformly mixed with 400 g of lactose, and a portion of the mixture was packed in a powder inhaler for exclusive use to produce a powder inhalant.

Preparation of a pharmaceutical composition: inhalation aerosol.

Formulation:

Compound of the present invention..... 200 μg

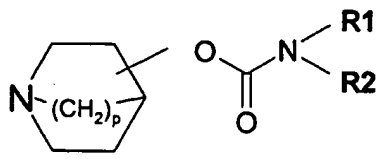
Dehydrated (Absolute) ethyl alcohol USP..... 8,400 μg

1,1,1,2-Tetrafluoroethane (HFC-134A)..... 46,810 μg

The active ingredient concentrate was prepared by dissolving 0.0480 g of the compound of the present invention in 2.0160 g of ethyl alcohol. The concentrate was added to an appropriate filling apparatus. The active ingredient concentrate was dispensed into an aerosol container, the headspace of the container was purged with nitrogen or HFC-134A vapour (purging ingredients should not contain more than 1 ppm oxygen) and was sealed with the valve. 11.2344 g of HFC-134A propellant was then filled into a sealed container.

CLAIMS

1. A compound which is a carbamate of formula (I):



(I)

wherein

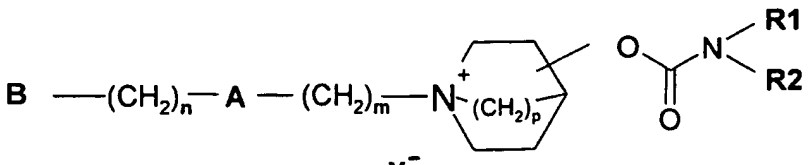
R1 represents a group selected from phenyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, benzyl, furan-2-ylmethyl, furan-3-ylmethyl, thiophen-2-ylmethyl, thiophen-3-ylmethyl;

R2 represents a group selected from optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkynyl, saturated or unsaturated cycloalkyl, saturated or unsaturated cycloalkylmethyl, phenyl, benzyl, phenethyl, furan-2-ylmethyl, furan-3-ylmethyl, thiophen-2-ylmethyl, thiophen-3-ylmethyl, pyridyl, and pyridylmethyl; wherein the carbocyclic moieties in the cycloalkyl, cycloalkylmethyl, phenyl, benzyl or phenethyl groups can be optionally bridged or fused to another saturated or unsaturated aromatic carbocyclic moiety or to a cyclic moiety comprising carbon atoms and 1 or 2 oxygen atoms;

the cyclic groups present in R_3 and R_4 being optionally substituted by one, two or three substituents selected from halogen, straight or branched, optionally substituted lower alkyl, hydroxy, straight or branched, optionally substituted lower alkoxy, -SH, straight or branched, optionally substituted alkylthio, nitro, –NR'R'', -CO_2R', -C(O)-NR'R'', -N(R''')C(O)-R', -N(R''')-C(O)NR'R'' or wherein R', R'' and R''' each independently represents a hydrogen atom or a straight or branched, optionally substituted lower alkyl group or R' and R'' together with the atom to which they are attached form a cyclic group;

p is 1 or 2 and the carbamate group is at positions 2, 3 or 4 of the azabicyclic ring,

and pharmaceutically acceptable salts thereof, including quaternary ammonium salts of formula (II)



(II)

wherein R1, R2 and p are as defined above;

m is an integer from 0 to 8;

n is an integer from 0 to 4;

A represents a group selected from $-CH_2-$, -CH=CR'-, -CR'=CH-, -CR'R''-, -C(O)-, -O-, -S-, -S(O)-, $-S(O)_2-$ and –NR'-, wherein R' and R'' are as defined above;

B represents a hydrogen atom, or a group selected from straight or branched, optionally substituted lower alkyl, hydroxy, straight or branched, optionally substituted lower alkoxy, cyano, nitro, -CH=CR'R'', -C(O)OR', -OC(O)R', -SC(O)R', -C(O)NR'R'', -NR'C(O)OR'', -NR'C(O)NR'', cycloalkyl, phenyl, naphthalenyl, 5,6,7,8-tetrahydronaphthalenyl, benzo[1,3]dioxolyl, heteroaryl or heterocyclyl; R' and R'' being as defined above; and wherein the cyclic groups represented by B are optionally substituted by one, two or three substitutuents selected from halogen, hydroxy, straight or branched, optionally substituted lower alkyl, phenyl, -OR', -SR', -NR'R'', -NHCOR', -CONR'R'', -CN, $-NO_2$ and -COOR'; R' and R'' being as defined above;

X^- represents a pharmaceutically acceptable anion of a mono or polyvalent acid;

including all stereoisomers of formulae (I) or (II) and mixtures thereof;

with the proviso that the compound of formula (I) is not one of

Diphenylcarbamic acid 1-azabicyclo[2.2.2]oct-3-yl ester

Ethylphenylcarbamic acid 1-azabicyclo[2.2.2]oct-3-yl ester.

2. A compound of formula (I) or formula (II) according to claim 1, wherein when the cyclic group present in R1 is unsubstituted or has only one substitutentsubstituent, R2 has at least one substituent.

3. A compound of formula (I) or formula (II) according to claim 1 wherein when R2 is not substituted the cyclic group present in R1 has at least two substituents.

4. A compound of formula (I) according to any one of claims 1 to 3, wherein when:

p is 2;

the carbamate group is attached at position 3 of the azabicyclic ring;

and R1 is an unsubstituted indanyl group or a phenyl group, which is optionally substituted with one or two substitutentsubstituents selected from chlorine, fluorine, bromine, methyl, hydroxy and cyano;

then R2 cannot be one of: unsubstituted cyclopropylmethyl; unsubstituted cyclobutylmethyl; unsubstituted cyclopentylmethyl; cyclohexylmethyl optionally substituted with a methyl or an isopropenyl group; unsubstituted cyclohexenyl; unsubstituted norbornenyl; unsubstituted bicyclo[2.2.1]heptanyl; unsubstituted benzo[1.3]dioxolyl; unsubstituted 2,3-dihydrobenzo[1.4]dioxinyl; unsubstituted benzyl; a benzyl group which is substituted with one or two substituents selected from fluorine, chlorine, bromine, methoxy, methyl, trifluoromethyl, ethyl, tertbutyl, hydroxy, hydroxymethyl, cyano, aminocarbonyl, trifluoromethoxy, benzyloxy, isopropyloxy; and a benzyl group which is substituted with three fluorine atoms.

5. A compound of formula (I) according to any one of claims 1 to 3 wherein R1 represents a group selected from 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, benzyl, furan-2-ylmethyl, furan-3-ylmethyl, thiophen-2-ylmethyl, thiophen-3-ylmethyl; the cyclic groups present in R1 being optionally substituted by one, two or three substituents selected from halogen, straight or branched, optionally substituted lower alkyl, hydroxy, straight or branched, optionally substituted lower alkoxy, -SH, straight or branched, optionally substituted lower alkylthio, nitro, cyano, –NR'R", $-CO_2R'$, -C(O)-NR'R", -N(R'")C(O)-R', -N(R'")-C(O)NR'R", wherein R', R" and R'" each independently represents a hydrogen atom or a straight or branched, optionally substituted lower alkyl group or R' and R" together with the atom to which they are attached form a cyclic group;

6. A compound of formula (I) according to any one of claims 1 to 3 wherein R2 represents an optionally substituted group selected from lower alkyl, lower alkenyl, lower alkynyl, saturated or unsaturated cycloalkyl, phenyl, phenethyl, furan-2-ylmethyl, furan-3-ylmethyl, thiophen-2-ylmethyl, thiophen-3-ylmethyl, pyridyl, and pyridylmethyl or a saturated or unsaturated cycloalkylmethyl group which has at least one substituent and is selected from substituted cyclopropylmethyl, substituted cyclobutylmethyl and substituted cyclopentylmethyl; the substituents of the cyclic groups present in R2 being one, two or three substituents selected from halogen, straight or branched, optionally substituted lower alkyl, hydroxy, straight or branched, optionally substituted lower alkoxy, -SH, straight or branched, optionally substituted lower alkylthio, nitro, cyano, -NR'R'', $-CO_2R'$, -C(O)-NR'R'', -N(R''')C(O)-R', -N(R''')-C(O)NR'R'', wherein R', R'' and R''' each independently represents a hydrogen atom or a straight or branched, optionally substituted lower alkyl group or R' and R'' together with the atom to which they are attached form a cyclic group;

7. A compound of formula (II) according to any one of claims 1 to 3 wherein when

p is 2;

the carbamate group is attached at position 3 of the azoniabicyclic ring having (3R)-configuration;

R1 is a phenyl group which is optionally substituted with a fluorine atom or a methyl group;

R2 is an unsubstituted cyclohexylmethyl group or a benzyl group which is optionally substituted with one or three fluorine atoms;

and X^- is iodine;

then, the sequence $B-(CH_2)_n-A-(CH_2)_m-$ cannot be a methyl group.

8. A compound of formula (II) according to any one of claims 1 or 2 with the proviso that the said compound is not one of:

(3R)-3-(Benzylphenylcarbamoyloxy)-1-methyl-1-azoniabicyclo[2.2.2]octane

iodide
(3R)-3-[(4-Fluorobenzyl)phenylcarbamoyloxy]-1-methyl-1-azoniabicyclo[2.2.2]octane iodide
(3R)-3-(Benzyl-o-tolylcarbamoyloxy)-1-methyl-1-azoniabicyclo[2.2.2]octane iodide
(3R)-1-Methyl-3-[o-tolyl-(2,4,5-trifluorobenzyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane iodide
(3R)-3-[(4-Fluorobenzyl)-m-tolylcarbamoyloxy]-1-methyl-1-azoniabicyclo[2.2.2]octane iodide
(3R)-3-[Benzyl-(2-fluorophenyl)carbamoyloxy]-1-methyl-1-azoniabicyclo[2.2.2]octane iodide
(3R)-3-[Cyclohexylmethyl-(2-fluorophenyl)carbamoyloxy]-1-methyl-1-azoniabicyclo[2.2.2]octane iodide.

9. A compound of formula (II) according to any one of claims 1 to 3, 7 or 8 wherein R1 represents a group selected from phenyl, 2-thienyl, 3-thienyl, thiophen-2-ylmethyl, thiophen-3-ylmethyl, furan-2-ylmethyl or furan-3-ylmethyl, the cyclic groups present in R1 being optionally substituted with one to three substitutentsubstituents selected from fluorine, chlorine, bromine, methyl, methoxy, trifluoromethyl, ethyl, tert-butyl, hydroxy and cyano.

10. A compound of formula (II) according to claim 9 wherein R1 represents a group selected from phenyl, 2-fluorophenyl, 3-flurorophenyl, 4-fluorophenyl, 3-methylphenyl, 4-methylphenyl, 2,5-difluorophenyl, 2,6-difluorophenyl, 2,4,5-trifluorophenyl, 5-methylfuran-2-ylmethyl, 4-fluoro-2-methylphenyl, 3-fluoro-4-methoxyphenyl, 3-methyl-thiophen-2-ylmethyl, 4,5-dimethylthiophen-2-ylmethyl, thiophen-3-ylmethyl, 5-methyl-furan-2-ylmethyl, 5-methyl-2-trifluoromethylfuran-3-ylmethyl, and 2,5-dimethylfuran-3-ylmethyl,

11. A compound of formula (II) according to any one of claims 1 to 3 or 7 to 10 wherein R2 represents a pent-4-enyl, pentyl, butyl, allyl, benzyl, thiophen-2-ylmethyl, thiophen-3-ylmethyl, furan-2-ylmethyl, furan-3-ylmethyl, phenethyl, cyclopentyl, cyclohexyl or cyclohexylmethyl group, the cyclic groups present R2 being optionally substituted with one to three substitutentsubstituents selected from fluorine, chlorine, bromine, methyl, methoxy, trifluoromethyl, ethyl, tert-butyl, hydroxy and cyano.

12. A compound according to claim 11 wherein R2 represents a group selected from 3-fluorobenzyl, 2,4,5-trifluorobenzyl, 3,4,5-trifluorobenzyl, 5-bromothiophen-2-

ylmethyl, 3,4-dimethoxyphenylethyl, 3-methylthiophen-2-ylmethyl, thiophen-3-ylmethyl, 4-bromo-5-methylthiophen-2-ylmethyl, 4,5-dimethylfuran-2-ylmethyl, furan-3-ylmethyl, 2-fluoro-4-methoxybenzyl, 2-(4-fluorophenyl)ethyl, butyl, pent-4-enyl and cyclopentyl.

13. A compound of formula (II) according to any one of claims 1 to 3 or 7 to 12 wherein A is $-CH_2-$, m and n are both 0, and B represents a group selected from straight or branched, optionally substituted lower alkyl, hydroxy, straight or branched, optionally substituted lower alkoxy, cyano, nitro, -CH=CR'R", -C(O)OR', -OC(O)R', -SC(O)R', -C(O)NR'R", -NR'C(O)OR", -NR'C(O)NR", cycloalkyl, phenyl, naphthanelyl, 5,6,7,8-tetrahydronaphthanelyl, benzo[1,3]dioxolyl, heteroaryl or heterocyclyl; R' and R" being as defined in claim1; and wherein the cyclic groups represented by B are optionally substituted by one, two or three substitutuents selected from halogen, hydroxy, straight or branched, optionally substituted lower alkyl, phenyl, -OR', -SR', -NR'R", -NHCOR', -CONR'R", -CN, $-NO_2$ and -COOR'; R' and R" being as defined above;

14. A compound of formula (II) according to any one of claims 1 to 3 or 7 to 12 wherein A is $-CH_2-$, B is as defined in claim 1 and at least one of m or n is not 0.

15. A compound of formula (II) according to any one of claims 1 to 3 or 7 to 12 wherein B represents a thiophen-2-yl group or a phenyl group which is optionally substituted with one to three substituents selected from halogen atoms, or hydroxy, methyl, $-CH_2OH$, -OMe, $-NMe_2$, -NHCOMe, $-CONH_2$, -CN, $-NO_2$, -COOMe, or $-CF_3$ groups.

16. A compound according to claim 15, wherein B represents a phenyl, 4-fluorophenyl, 3-hydroxyphenyl or thiophen-2-yl group.

17. A compound of formula (II) according to any one of claims 1 to 3, 7 to 12, 15 or 16 wherein n= 0 or 1; m is an integer from 1 to 6; and A represents a $-CH_2-$, -CH=CH-, -CO-, -Nme-, -O- or -S- group.

18. A compound of formula (II) according to claim 17, wherein m is 1, 2 or 3 and A represents a $-CH_2-$, -CH=CH-, or –O- group.

19. A compound of formula (II) according to any one of claims 1 to 3 or 7 to 12 wherein the sequence $B-(CH_2)_n-A-(CH_2)_m-$ represents a group selected from

3-phenoxypropyl, 2-phenoxyethyl, 3-phenylallyl, phenethyl, 3-phenylpropyl, 3-(3-hydroxyphenoxy)propyl, 3-(4-fluorophenoxy)propyl, 3-thiophen-2-ylpropyl, allyl, heptyl, 3-cyanopropyl and methyl.

20. A compound of formula (II) according to any one of claims 1 to 3 or 7 to 19 wherein X^- represents a chloride, bromide, trifluoroacetate or methanesulphonate anion.

21. A compound of formula (I) or (II) according to any one of the preceding claims, wherein p is 2.

22. A compound of formula (I) or (II) according to any one of the preceding claims, wherein the azabicyclic ring is substituted in the 3-position.

23. A compound of formula (I) or (II) according to claim 22 wherein the carbon at the 3-position of the azabicyclic ring has R configuration.

24. A compound of formula (I) or (II) according to claim 22 wherein the carbon at the 3-position of the azabicyclic ring has S configuration.

25. A compound according to any one of the preceding claims, which is a single isomer.

26. A compound of formula (I) according to claim 1 which is one of:

[2-(3,4-Dimethoxyphenyl)ethyl]-(5-methylfuran-2-ylmethyl)carbamic acid (3R)-1-azabicyclo[2.2.2]oct-3-yl ester

(5-Bromothiophen-2-ylmethyl)-(2,4,5-trifluorophenyl)carbamic acid (3R)-1-azabicyclo[2.2.2]oct-3-yl ester

(4-Fluoro-2-methylphenyl)-(3-methylthiophen-2-ylmethyl)carbamic acid (3R)-1-azabicyclo[2.2.2]oct-3-yl ester

(3-Fluoro-4-methoxyphenyl)thiophen-3-ylmethylcarbamic acid (3R)-1-azabicyclo[2.2.2]oct-3-yl ester

Thiophen-3-ylmethyl-(2,4,5-trifluorobenzyl)carbamic acid (3R)-1-azabicyclo[2.2.2]oct-3-yl ester

(4-Bromo-5-methylthiophen-2-ylmethyl)-(3-methylthiophen-2-ylmethyl)carbamic acid (3R)-1-azabicyclo[2.2.2]oct-3-yl ester

(4,5-Dimethylfuran-2-ylmethyl)-(5-methylfuran-2-ylmethyl)carbamic acid (3R)-1-azabicyclo[2.2.2]oct-3-yl ester
Furan-3-ylmethyl-(5-methyl-2-trifluoromethylfuran-3-ylmethyl)carbamic acid (3R)-1-azabicyclo[2.2.2]oct-3-yl ester
(2,5-Dimethylfuran-3-ylmethyl)-(2-fluoro-4-methoxybenzyl)carbamic acid (3R)-1-azabicyclo[2.2.2]oct-3-yl ester
[2-(4-Fluorophenyl)ethyl]-(3-methylthiophen-2-ylmethyl)carbamic acid (3R)-1-azabicyclo[2.2.2]oct-3-yl ester
Butyl-(2,5-difluorophenyl)carbamic acid (3R)-1-azabicyclo[2.2.2]oct-3-yl ester
(2,6-Difluorophenyl)pent-4-enylcarbamic acid (3R)-1-azabicyclo[2.2.2]oct-3-yl ester
Cyclopentyl-(4,5-dimethylthiophen-2-ylmethyl)carbamic acid (3R)-1-azabicyclo[2.2.2]oct-3-yl ester

27. A compound of formula (II) according to claim 1 which is one of:

(3R)-3-[(3-Fluorobenzyl)-(3-fluorophenyl)carbamoyloxy]-1-(2-phenoxyethyl)-1-azoniabicyclo[2.2.2]octane bromide
(3R)-3-[(3-Fluorobenzyl)-(3-fluorophenyl)carbamoyloxy]-1-(3-phenylpropyl)-1-azoniabicyclo[2.2.2]octane bromide
(3R)-1-(2-Phenoxyethyl)-3-[m-tolyl-(2,4,5-trifluorobenzyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane bromide
(3R)-1-(3-Phenylpropyl)-3-[m-tolyl-(2,4,5-trifluorobenzyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane bromide
(3R)-3-[(3-Fluorophenyl)-(3,4,5-trifluorobenzyl)carbamoyloxy]-1-(2-phenoxyethyl)-1-azoniabicyclo[2.2.2]octane bromide
(3R)-1-Allyl-3-[[2-(3,4-dimethoxyphenyl)ethyl]-(5-methylfuran-2-ylmethyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane bromide
(3R)-3-[(5-Bromothiophen-2-ylmethyl)-(2,4,5-trifluorophenyl)carbamoyloxy]-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane trifluoroacetate
(3R)-3-[[2-(3,4-dimethoxyphenyl)ethyl]-(5-methylfuran-2-ylmethyl)carbamoyloxy]-1-(4-ethoxycarbonylbutyl)-1-azoniabicyclo[2.2.2]octane trifluoroacetate
(3R)-3-[(4-Fluoro-2-methylphenyl)-(3-methylthiophen-2-ylmethyl)carbamoyloxy]-1-(2-phenoxyethyl)-1-azoniabicyclo[2.2.2]octane trifluoroacetate
(3R)-3-[(3-Fluoro-4-methoxyphenyl)thiophen-3-ylmethylcarbamoyloxy]-1-(3-phenylallyl)-1-azoniabicyclo[2.2.2]octane trifluoroacetate
(3R)-1-Phenethyl-3-[thiophen-3-ylmethyl-(2,4,5-trifluorobenzyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane trifluoroacetate

(3R)-3-[(4-Bromo-5-methylthiophen-2-ylmethyl)-(3-methylthiophen-2-ylmethyl)carbamoyloxy]-1-(3-phenylpropyl)-1-azoniabicyclo[2.2.2]octane trifluoroacetate

(3R)-3-[(4,5-Dimethylfuran-2-ylmethyl)-(5-methylfuran-2-ylmethyl)carbamoyloxy]-1-[3-(3-hydroxyphenoxy)propyl]-1-azoniabicyclo[2.2.2]octane trifluoroacetate

(3R)-1-[3-(4-Fluorophenoxy)propyl]-3-[furan-3-ylmethyl-(5-methyl-2-trifluoromethylfuran-3-ylmethyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane trifluoroacetate

(3R)-3-[(2,5-Dimethylfuran-3-ylmethyl)-(2-fluoro-4-methoxybenzyl)carbamoyloxy]-1-(3-thiophen-2-ylpropyl)-1-azoniabicyclo[2.2.2]octane trifluoroacetate

(3R)-1-Allyl-3-[2-(4-fluorophenyl)ethyl]-(3-methylthiophen-2-ylmethyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane trifluoroacetate

(3R)-3-[Butyl-(2,5-difluorophenyl)carbamoyloxy]-1-heptyl-1-azoniabicyclo[2.2.2]octane trifluoroacetate

(3R)-1-(3-Cyanopropyl)-3-[(2,6-difluorophenyl)pent-4-enylcarbamoyloxy]-1-azoniabicyclo[2.2.2]octane trifluoroacetate

(3R)-3-[Cyclopentyl-(4,5-dimethylthiophen-2-ylmethyl)carbamoyloxy]-1-methyl-1-azoniabicyclo[2.2.2]octane trifluoroacetate

28. A pharmaceutical composition comprising a compound according to any one of claims 1 to 27 in admixture with a pharmaceutically acceptable carrier or diluent.

29. A compound according to any one of claims 1 to 27 for the treatment of a pathological condition or disease susceptible to amelioration by antagonism of M3 muscarinic receptors.

30. Use of a compound according to any one of claims 1 to 27 in the manufacture of a medicament for the treatment of a pathological condition or disease susceptible to amelioration by antagonism of M3 muscarinic receptors.

31. Use according to claim 30 wherein the pathological condition is a respiratory, urological or gastrointestinal disease or disorder.

32. A method for treating a subject afflicted with a pathological condition or disease susceptible to amelioration by antagonism of M3 muscarinic receptors, which comprises administering to said subject an effective amount of a compound as defined in any one of claims 1 to 27.

33. A method according to claim 32 wherein the pathological condition is a respiratory, urological or gastrointestinal disease or disorder.

34. A combination of products comprising
(i) a compound according to any one of claims 1 to 27; and
(ii) another compound effective in the treatment of a respiratory, urological or gastrointestinal disease or disorder
for simultaneous, separate or sequential use.

35. A combination product according to claim 34 comprising
(i) a compound according to any one of claims 1 to 27; and
(ii) a $ß_2$ agonist, steroid, antiallergic drug, phosphodiesterase IV inhibitor and/or leukotriene D4 (LTD4) antagonist
for simultaneous, separate or sequential use in the treatment of a respiratory disease.